Appeal Nos. CA-2024-002325 & CA-2024-002295

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT (The Hon Mr Justice Meade)

Claim No: HP-2022-000022

BETWEEN:

MODERNATX, INC.

Claimant / Respondent

– and –

(1) PFIZER LIMITED
(2) PFIZER MANUFACTURING BELGIUM NV
(3) PFIZER INC.
(4) BIONTECH MANUFACTURING GMBH
(5) BIONTECH SE

Defendants / Appellants

AND BETWEEN:

Claim No: HP-2022-000027

(1) PFIZER INC.
(2) BIONTECH SE

Claimants / Appellants

– and –

MODERNATX, INC.

Defendant / Respondent

PFIZER / BIONTECH'S SKELETON ARGUMENT

References to the Appeal Bundles are in the form [Bundle/Tab/Page]

10 April 2025

TOM MITCHESON KC
ALICE HART

Instructed by Taylor Wessing LLP for Pfizer

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Instructed by Powell Gilbert LLP for BioNTech

INTRODUCTION

1. This is an appeal from the judgment of Meade J dated 2 July 2024 (the "**Judgment**"),[1] which addressed the validity of two of Moderna's patents termed EP949 and EP565. The Judge found that EP949 was novel and not obvious. Permission to appeal both findings was given by the Judge on the basis of the Grounds of Appeal in the Core Bundle. EP565 was found to be invalid; Moderna was refused permission to appeal so we say no more about it. [CORE/5]

2. As the Judge explained at §12, these proceedings were brought against the background of the Covid-19 pandemic and Pfizer/BioNTech's range of Comirnaty® mRNA vaccines. There are no issues on infringement. [CORE/5/51]

3. This case concerns mRNA that is modified to improve its properties. These modifications improve its translational capacity (i.e. ability to make whatever protein it encodes) and suppress the innate immune response, which is otherwise stimulated when exogenous RNA is introduced into cells and triggers pathways that act to reduce protein production and/or destroy the cells.

4. EP949 concerns mRNA containing a particular modified nucleotide – N1-methylpseudouridine (m1Ψ) – in place of the naturally occurring uridine (U). The relevant claims before the Judge are product claims to a molecule of mRNA:

> **3.** An mRNA wherein 100% of nucleotides comprising uracil in the mRNA are replaced with nucleotides comprising N1-methyl-pseudouridine.
>
> **5.** An mRNA according to [claim 3] comprising a polyA tail.

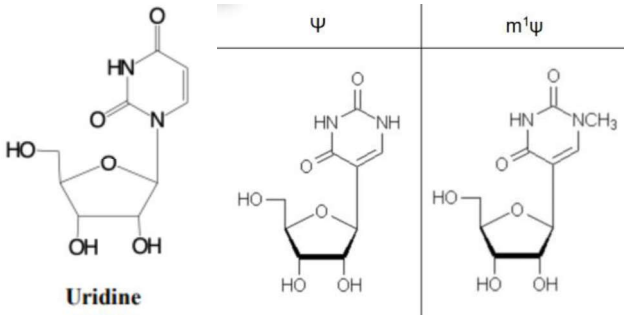
5. Thus, an mRNA molecule *per se* is the target for the invalidity analysis. All that is required is that the molecule be disclosed by the prior art, or that it be obvious to make in the light of that prior art. Although the Judge dealt with it, the status of claim 5 is unclear because the equivalent claim does not form part of Moderna's set of claim requests pending before the TBA of the EPO. Moderna's main request, as allowed by the OD, is a single claim identical to claim 3 above.

6. It was common general knowledge (CGK) at the priority date that exogenous RNA stimulated the innate immune response and that modified nucleotides could suppress such a response. The CGK included a 2005 paper from the group of Katalin Karikó

[1] References herein to paragraphs (§) are to the Judgment, unless otherwise stated.

and Drew Weissman at the University of Pennsylvania, which showed, in particular, that replacement of U with naturally occurring chemical modifications of U, including pseudouridine (Ψ), could reduce the immunogenicity of mRNA (§§240-248). [CORE/5/99-100]

7. EP949 does not show that m1Ψ is superior to Ψ, as Moderna accepted (§§287 & 422). [CORE/5/108&135] So the technical contribution of the patent, and what is said by Moderna to be its invention worthy of a 20-year monopoly, is the provision of mRNA containing an alternative modification to Ψ, namely a methylated derivative, m1Ψ. The structures of U, Ψ and m1Ψ are shown in the Judgment at §§202 and 306: [CORE/5/94 & 114]



8. Pfizer/BioNTech relied upon two items of prior art at trial: a patent application known as UPenn (cited for novelty and obviousness) and a paper, Karikó 2008 (cited for obviousness only). Each derives from the Karikó/Weissman group, building on the group's 2005 work (see paragraph 6 above) and presenting data showing that mRNA containing Ψ in place of U not only demonstrates reduced immunogenicity but also improved translation. Karikó and Weissman were awarded the 2023 Nobel Prize for medicine for this work.[2]

9. The oddity of this case is that Moderna's alternative modification is expressly disclosed in UPenn. m1Ψ is one of the five Ψ-like modifications disclosed in [0056]. It is also disclosed in Example 31, which teaches the reader to make and test additional modifications. BioNTech took a licence under the granted version of UPenn and has paid very substantial royalties under it. Moderna is also a licensee.

10. As we explain below, the Judge should have found that the claims are not novel, alternatively that there is no invention in following the instructions in UPenn to test other modifications, including the derivatives of Ψ picked out in [0056], especially if seeking only to identify an alternative to Ψ. We address the Grounds in that order.

[2] https://www.nobelprize.org/prizes/medicine/2023/press-release/, which cites both the 2005 and 2008 papers, and a later 2010 paper. [SUPP/22]

NOVELTY OVER UPENN (GROUNDS 4, 5 & 6)

The law of novelty

11. For a patent to be deprived of novelty, the prior art must both disclose the claimed subject matter and enable the skilled person to perform that subject matter: see *Synthon v SmithKline Beecham Plc (No.2)* [2006] 1 All ER 685 at [22]-[24]. [JA/5/231-232]

12. The issue in the present case, and where the Judge fell into error, is what the prior art discloses; there is no dispute about enablement.

13. The Judge correctly identified the disclosure test for novelty, which requires that the subject matter be "*directly and unambiguously derivable*" from the prior art, alternatively that the prior art contains "*clear and unmistakeable directions"* to do what the patentee claims to have invented (§§122-123). [CORE/5/74]

14. Where the prior art discloses lists or groups of compounds, one test which has emerged from EPO jurisprudence and can be used to determine whether or not the claimed subject matter is "*directly and unambiguously derivable*" from the prior art is to analyse whether there is a sufficiently *"individualised description"* of the claimed compound to be disclosed.

15. The Judge referred to this Court's decision in *Dr Reddy's v Eli Lilly* [2010] RPC 9, which explored the concept of an "*individualised description*" (§§128-129). In that case, the presence of olanzapine amongst the 10^{19} compounds of formula (I) in the prior art was not novelty destroying because it was found not to be individually described.[3] As Jacob LJ held, the case was *"miles from that"* ([30]). [JA/8] [CORE/5/75-78] [JA/8/339-340]

16. The Judge described the EPO case of *Hoechst* T 296/87 as being one "*at the other end of the spectrum"* from *Dr Reddy's* (§130). In that case, the disclosure of a racemate (a mixture of two enantiomers) was held not to be a disclosure of a single enantiomer. However, *Hoechst* does not stand for the principle that where the list of options in the prior art is small (there, two), novelty is nonetheless not destroyed. Rather, it is a case where the disclosure of a racemate was held not to be the disclosure of an enantiomer because nowhere was there an individualised description of the constituent enantiomers. [JA/18] [CORE/5/78]

[3] The superscript on the "19" has been lost in the Judge's quote from *Dr Reddy's* at §128. [CORE/5/75]

17. So when the Board in *Hoechst* refers (in the quote at [30] of *Dr Reddy's* at the Judge's §128) to the distinction between "*the purely intellectual content of an item of information"* and *"the material disclosed in the sense of a specific teaching"*, it is referring to the fact that while it would be known "*intellectually*" that enantiomers exist within the racemate, a specific teaching of a particular enantiomer would be required for it to be disclosed. One must therefore be cautious in seeking to characterise *Hoechst* as a case "*at the other end of the spectrum*" from *Dr Reddy's*"; its context was quite different (and quite specific). [JA/8/339-340] [CORE/5/75]

18. The final case referred to by the Judge was *Almirall v Boehringer* [2009] FSR 12 at [217]-[222] (§130). In that case, the 159 examples of the prior art *were* found to be sufficiently "*individualised*" and the novelty attack only failed because of the "*bewildering list of choices"* required to select the additional elements of the claim (albeit they were obvious). [JA/7/307-308] [CORE/5/78]

19. Another test that can be used to determine whether or not the claimed subject-matter is "*directly and unambiguously derivable*" from the prior art, which is used at the EPO, is to analyse whether the subject matter of the claim is arrived at by selection of features from multiple independent lists in the prior art, as summarised by the Judge at §§132-144. No criticism is made of this summary of the EPO law. A point arises on §145 and the need for *independent* lists, which is picked up in context below. [CORE/5/78-80] [CORE/5/80]

20. Pfizer/BioNTech advanced three "routes" on novelty over UPenn at trial: Routes 1 and 2 (starting from Example 31) and Route 3 (starting from claim 1/[004] and [0056]). These are dealt with in reverse order below, starting first with the interpretation of [0056] since that was central to the Judge's analysis. As can be seen, despite having correctly identified the disclosure test for novelty, the Judge failed to apply that test appropriately to the facts, instead applying too strict a standard as to what was required to feature in the prior art for novelty to be destroyed. [SUPP/2/88& 96-97]

Construction of [0056] of UPenn

21. UPenn is a patent application from Karikó and Weissman, who were already well known for their work in this field from their 2005 paper (see above). [0056] of UPenn discloses m1Ψ in a short list of Ψ-like modified nucleotides. It states as follows (full chemical names excluded from the quote for brevity and emphasis added): [SUPP/2/96-97]

> "Pseudouridine" refers, in another embodiment, to $m^1acp^3\Psi$… In another embodiment, the term refers to $m^1\Psi$… In another embodiment, the term refers to Ψm… In another embodiment, the term refers to m^5D… In another embodiment, the term refers to $m^3\Psi$… In another embodiment, the term refers to a pseudouridine moiety that is not further modified. In another embodiment, the term refers to a monophosphate, diphosphate, or triphosphate of any of the above pseudouridines. In another embodiment, the term refers to any other pseudouridine known in the art. Each possibility represents a separate embodiment of the present invention.

22. The meaning of [0056] must not, however, be considered in isolation. It must be considered in the context of the entire document and through the eyes of the skilled reader. [SUPP/2/96-97]

23. [001] states that the invention provides RNA molecules "*comprising pseudouridine or a modified nucleoside*". This is also reflected in claim 1 and [004], which disclose an mRNA "*comprising a pseudouridine residue*" (emphasis added). [SUPP/2/87] [SUPP/2/88]

24. UPenn contains data on a handful of modified nucleosides and their effect on immunogenicity and/or translation. There are most data on Ψ. The data on Ψ are very promising and Ψ is the best-performing nucleoside of those tested (§§360(i) & 361). [CORE/5/123-124]

25. UPenn contains three lists of modified nucleosides, namely:

    (a) [0056], which states that "*"Pseudouridine" refers*" to the Ψ-like modifications, namely m1acp3Ψ, m1Ψ, Ψm, m5D and m3Ψ, each expressly being "*another embodiment*"; [SUPP/2/96-97]

    (b) [0069], which states that "*the modified nucleoside of methods and compositions of the present invention is*" m5C, m5U, m6A, s2U, Ψ or Um, again each expressly being *"another embodiment"*; and [SUPP/2/99]

    (c) [0070], which states that *"In other embodiments, the modified nucleoside is"* and lists the remaining 92 naturally occurring modified nucleosides. [SUPP/2/100]

26. There are therefore two short lists ([0056] and ([0069]) and one longer list ([0070]). [SUPP/2/96-97&99&100]

27. As the Judge rightly found, the skilled reader would realise that [0069] was a list of the nucleosides tested in the UPenn Examples (§375). Ψ is the only pseudouridine in that list, the other molecules being modifications of different bases or modifications of uracil which are not pseudouridines. [SUPP/2/99] [CORE/5/125]

28. The skilled reader would also realise that [0056] was the only other short list of nucleosides specifically called out by the authors. This begs the following questions for the skilled reader: Why are these nucleosides specifically called out in [0056]?

29. In light of (i) the very promising data on Ψ, (ii) the Ψ-like modifications in [0056] being the only shortlist of nucleosides picked out that the authors had not already tested and (iii) the reference in [004] and claim 1 to "*a messenger RNA comprising a pseudouridine residue"*, [0056] would be understood by the skilled reader as a matter of disclosure as presenting a preferred list of Ψ-like modified nucleosides. [SUPP/2/96-97] [SUPP/2/88] [SUPP/2/96-97]

30. The Judge described [0056] as "*an odd creature because it is a definition section and not an expression of any technical preference for the listed nucleotides*" (§335) and "*a definition not a scientific statement*" (§379(i)). [CORE/5/118-119] [CORE/5/127]

31. This is one of the places he fell into error, whether it is seen as a "definition" section or not. In construing [0056] this way, the Judge failed properly to consider the meaning and effect of [0056] to the skilled reader in the context of the wider disclosure of the whole document, including the promising results seen with Ψ itself. Had he done so, he would have found that, when read together with [004] and claim 1 in particular, [0056] provided a clear disclosure of the Ψ-like nucleotides of particular interest. [SUPP/2/96-97] [SUPP/2/96-97]

32. This error fed into the Judge's novelty analysis, as explained below.

Route 3 – claim 1/[004] of UPenn

33. Novelty Route 3 starts with [004] or claim 1, each of which discloses an mRNA comprising a pseudouridine residue. The Judge correctly found that either is a legitimate starting point for the novelty analysis (§335). [SUPP/2/88] [CORE/5/118-119]

34. We have addressed [0056] above; it lists Ψ itself and a short selection of Ψ-like compounds (m1acp3Ψ, m1Ψ, Ψm, m5D and m3Ψ) as embodiments of "*pseudouridine*". It also refers to "*any other pseudouridine known in the art*" – there was in fact none, but this is dealt with further below since the Judge placed some weight on it.

35. Claim 1 of UPenn, read together with [0056], therefore discloses mRNA where U is replaced by m1Ψ. 100% replacement (i.e., that 100% of the Us are replaced by m1Ψs) is disclosed at [0074] and there are multiple strong "pointers" to this choice of [SUPP/2/102]

percentage, not least because it would be the "default" choice in any IVT reaction. It is in any event not an "independent" choice or list since one *must* choose *a* percentage when making mRNA with U replacements – see further below.

36. The Judge rejected these arguments for the reasons given at §§335-339. The following were the errors in his analysis. [CORE/5/118-119]

37. First, the Judge considered that [0056] was *"not an expression of any technical preference for the listed nucleotides"*.

38. However, before one even considers the correct meaning of [0056], the Judge was wrong to require that there be any "*technical preference*" for the [0056] nucleosides in order for them to be disclosed or read into claim 1/[004]. He rightly found that both claim 1 and [004] "*lead to [0056]*", presumably by reason of their reference to "*pseudouridine*" and [0056] being directed to what pseudouridine *"refers*" (§335). No further preference or pointer to [0056] is needed for the purposes of the test for disclosure. [SUPP/2/88 & 161] [CORE/5/118]

39. To the extent a "*technical preference*" for the [0056] nucleosides is needed, we dealt with the reasons why [0056] would, in fact, be understood as teaching such a preference above including that, as the Judge found, the data on Ψ are very promising and Ψ is the best-performing nucleoside of those tested.

40. However, even if the Judge was right that [0056] is properly characterised as "*a definition*", then it follows that it must operate as a definition of "*pseudouridine"* in the document. As such, the skilled reader would understand that m1Ψ was "*a pseudouridine residue*" within the scope of claim 1 and novelty would be destroyed on that analysis too.

41. Second, the Judge found that, by reason of the reference to "*any other pseudouridine known in the art"* in [0056], the list was "*open-ended"* and *"unclear"* (§§335, 339 & 379(iii)). [CORE/5/118-119 &127]

42. But as the Judge rightly found, the skilled person could discover from the RNA Modification Database (RNAMD) (agreed to be CGK (see §§200 & 250) and expressly referred to in [002] of UPenn) that there were in fact no known naturally occurring pseudouridines other than those listed in [0056] (§§335 & 383). Dr Enright's evidence was thus that there was no other "*pseudouridine known in the art"* [CORE/5/94 & 100] [CORE/5/118-119 &128]

(Enright 1 §7.15), a point with which Moderna's expert, Prof Rosenecker, did not take issue. [SUPP/9/223]

43. The skilled reader would therefore have understood that the list in [0056] was not open-ended. The Judge was wrong to characterise the use of the RNAMD in this context as "*a process of research and deduction plugging in aspects of the CGK, not part of the disclosure of UPenn*" (§335). It is a classic example of the skilled person using their CGK to understand the disclosure of the document. The Judge also had no basis upon which to go further and suggest that the skilled person would not know that there were *"no* [other pseudouridines] *in the world"* (§335; see also §379(iii)). Neither expert suggested that the skilled person would think that there were other pseudouridines. Nor did either expert take the view that the [0056] list was "*unclear*". [CORE/5/118-119] [CORE/5/118 & 127]

44. Finally, the Judge referred in §335 to pseudouridines "*that might be found in the future*". It is well-established that a prior art document should be construed at the date of its publication: see Sachs LJ in *General Tire & Rubber Co v Firestone Tyre & Rubber Co* [1971] FSR 417 at 443. The reliance by the Judge on pseudouridines not yet known to support the suggestion that the list is open-ended and/or unclear is therefore misplaced. He appeared to be straining to find the claim novel. [CORE/5/118-119]

45. None of the above takes away from the fact that m1Ψ is clearly and unambiguously disclosed in [0056] as part of a short list and is also therefore individualised. However, the Judge appeared to require something more in §336, relying upon the further fact that *"m1Ψ is not said to be preferred"*. This is a prime illustration of the Judge's improperly strict approach to novelty, and the Judge gives no reasons in §336 for requiring that m1Ψ be preferred. [CORE/5/119]

46. [0056] discloses each of m1acp3Ψ, m1Ψ, Ψm, m5D and m3Ψ. The law does not require that m1Ψ be picked out as "*preferred*" to the exclusion of the others in [0056] in order for it to be disclosed. The test is not whether the claimed compound is individualised to the exclusion of everything else; prior art may individually describe multiple compounds that would destroy the novelty of a patent claiming any one of them – see *Dr Reddy's/Almirall*.

47. The question the Judge should have asked himself is whether or not m1Ψ is disclosed in [0056]. The answer is that it plainly is. Read together with claim 1/[004], UPenn discloses an mRNA containing m1Ψ in place of U. [SUPP/2/88 & 161]

48. The Judge's third error concerned the 100% replacement element of the claim, addressed at §§337-338, wherein he found that the pointers to full replacement were not strong. [CORE/5/119]

49. Being the "default" in any IVT reaction, 100% replacement would have been assumed by the skilled reader upon reading claim 1/[004], but it is in any event disclosed in [0074] as one of a number of possibilities. [SUPP/2/88 & 161] [SUPP/2/102]

50. Further, if the skilled person synthesised a molecule of claim 1/[004] using m1Ψ from [0056] and followed the method of synthesis taught in the document, namely that in Example 2, 100% replacement would result (as the Judge rightly found (§§315 & 337)). They would thus inevitably arrive at the claimed molecule. [CORE/5/115 & 119]

51. There is in any event no question that 100% replacement would be preferred, since:

(a) As noted above, Example 2 describes a method for synthesis of modified RNAs, and the method it describes leads to 100% replacement (§§315 & 337); [SUPP/2/131-134] [CORE/5/115 & 119]

(b) Example 7 of UPenn teaches that 100% replacement results in the greatest effect in terms of a reduction in innate immune response (see also Figure 5); and [SUPP/2/138-140] [SUPP/2/174]

(c) It was known as a matter of CGK that it would be technically easier and more reliable than other possibilities, as the Judge rightly found (§337; see Enright 1 §7.21 for the reasons why)). Further, it was CGK that immune suppression was proportional to the % of modifications (§251(i)). [CORE/5/119] [SUPP/9/224] [CORE/5/100]

52. The Judge relied upon the fact that it is not clear from Example 2 (alone) that 100% is necessarily preferred as "*a lesser percentage might be just as good*" (§337). However, the teaching of UPenn must be interpreted as a whole and Example 7 clearly shows that a lesser percentage is *not* just as good. [CORE/5/119] [SUPP/2/138-140]

53. When it came to considering Example 7, the Judge dismissed this by finding that *"that is not the same as saying that 100% would be necessary"* (§337). Necessity is not the correct standard for a "pointer" in this context. It is enough that the disclosure of UPenn teaches that 100% replacement is technically preferred, which it does for the reasons we have given. [CORE/5/119]

54. Further, there is no requirement for "*analysis*" to arrive at this answer, as the Judge found in §338; this preference would be immediately apparent to the skilled reader. Nor is there a need for there to be a "*direct link*" to the [0074] list, as he also found. [CORE/5/119] [SUPP/2/9]

There was never any suggestion that the skilled reader would not understand that the subject matter of Example 7 related to the kinds of percentage replacements disclosed in [0074].

55. Finally, the choice of percentage replacement is not a choice that is *independent* from the selection of a modified nucleotide in the sense that the EPO refers to dependent and independent lists. This is because a scientist choosing to synthesise an mRNA containing m1Ψ in place of U necessarily has to choose a percentage of modified nucleotide to use and so it is not an option not to go at all to that "list". The Judge was wrong to find to the contrary and/or to hold that the EPO case law did not support this principle (§145). See T1581/12 referred to by the Judge, T1259/16 at [21]-[41], T783/09 at [5]-[6] and see also Birss J in *Novartis v Dr Reddy's* [2019] EWHC 92 (Pat) at [29]. [CORE/5/80-81] [JA/21] [JA/22/895-901] [JA/20/822-827] [JA/12/539]

56. A "selection from independent lists"-type analysis is therefore not appropriate for this claim. The Judge's consideration in §339 of the lack of any disclosure of a pointer to the *combination* of m1Ψ and 100% replacement is therefore misplaced. [CORE/5/119]

57. As regards claim 5 of EP949, this contains the additional requirement that the mRNA comprises a polyA tail. As noted above, we cannot see how claim 5 can ultimately assist Moderna because one way or another it will be deleted by the TBA at the EPO. Nevertheless, claim 2 of UPenn claims "[A messenger RNA comprising a pseudouridine residue] *further comprising a poly-A tail"*. The same arguments as set out above starting from claim 1 apply. Further, a polyA tail would plainly be preferred because of the combination of claims 1 and 2 and since it was CGK that mature eukaryotic mRNA generally has a polyA tail, increasing its stability and promoting its translation (see §186). Example 12 of UPenn additionally shows that addition of a polyA tail further enhances translation. [SUPP/1/52] [SUPP/2/161] [CORE/5/90-91]

58. For all these reasons the Judge was wrong to hold that the claims were novel.

Routes 1 & 2 – Example 31 of UPenn

59. The alternative routes to anticipation start with Example 31. [SUPP/2/160]

60. Example 31 is entitled "*Testing the effect of additional nucleoside modifications on RNA immunogenicity and efficiency of translation*". The text then states as follows:

[00290] Additional nucleoside modifications are introduced into *in vitro*-transcribed RNA, using the methods described above in Examples 2 and 7, and their effects on immunogenicity translation efficiency are tested as described in Examples 1-8 and 9-15, respectively. Certain additional modifications are found to decrease immunogenicity and enhance translation. These modifications are additional embodiments of methods and compositions of the present invention. [SUPP/2/119] [SUPP/2/131-134 & 138-140] [SUPP/2/128-146]

61. Example 31 thus provides a clear description of instructions to make (using the methods described in Examples 2 and 7) mRNA containing certain additional nucleoside modifications and to test (as described in Examples 1-8 and 9-15) their effect on both immunogenicity and translation efficiency.

62. Example 2 is entitled *"In vitro synthesis of RNA molecules with modified nucleosides"*. It describes experiments to generate "*the following long RNAs:… RNA-1866… RNA-1571… RNA-730… RNA-713… RNA-497*" ([00187]). [00194] states that *"Several sets of RNA with different primary sequences... were transcribed"*. This includes RNA-1866, an mRNA with a poly-A tail (§326). As discussed above, Example 2 teaches 100% replacement ([00193]-[00194]; §315). [SUPP/2/131] [SUPP/2/134] [CORE/5/117] [CORE/5/115] [SUPP/2/134]

63. Returning to Example 31, [00291] then states: "*Modifications tested include, e.g.*" and lists 96 modified nucleosides. This list corresponds to the [0056] list (Ψ and Ψ-like nucleosides) and [0070] list (other nucleosides) and excludes the six modifications made and tested in the previous Examples (i.e., the [0069] list). [SUPP/2/160] [SUPP/2/100-101] [SUPP/2/99]

64. Pfizer/BioNTech contend that Example 31 individually discloses each of its 96 members, including m1Ψ (cf. the 159 individualised examples in *Almirall)*. Carrying out Example 31 with m1Ψ involves carrying out Example 2, which results in the skilled person making an mRNA of claims 3 and 5 of EP949. This is Route 1. [SUPP/1/52]

65. Route 2 arises if, contrary to the above, the skilled reader would need to make a selection from the RNAs in Example 2 to arrive at an mRNA (since all but one of the Example 2 RNAs are mRNA (§314)). If that is the case, Pfizer/BioNTech relies on various pointers to selection of mRNA, as discussed below. [CORE/5/115]

66. The Judge rejected these arguments for the reasons given at §§321-329. The following were the errors in his analysis. [CORE/5/116-118]

67. First, having correctly found that it is not necessary for anticipation that something has actually been done, and so a prospective example can be novelty-destroying, the

Judge found that Example 31 *"is extremely tentative and open ended"* (§323; see also §321(iii)) and that *"all Example 31 is saying in relation to Examples 2 and 7, at least with any clarity, is that they provide methods that may be used. I do not see any teaching in Example 31 to go back and redo Example 2 or Example 7 with the exact RNA sequences disclosed there"* (§324). [CORE/5/117] [CORE/5/116] [CORE/5/117]

68. This is wrong as a matter of construction of Example 31. The text of [00290] states explicitly that additional nucleoside modifications are introduced into *in vitro*-transcribed RNA using the methods described in Examples 2 and 7. It does not say that the methods in Examples 2 and 7 *may* be used. The language is not tentative, let alone extremely so. The unambiguous instructions are to go back and perform Examples 2 and 7 with additional modifications. [SUPP/2/160]

69. Similarly, the Judge was wrong to find in §323 that the *"extent of what* [Example 31] *is proposing and the reasons for doing it are both woolly (see Jacob LJ in Dr Reddy's at [31])"*. The reasons for testing additional modifications would be clear to the skilled reader. UPenn is a document all about the role of nucleoside modifications on the immunogenicity and translation efficiency of RNA (see [002]). It tests those properties for a handful of nucleosides in Examples 1 to 15. Example 31 then describes experiments to replicate those experiments to test those properties for additional modifications, stating that "*Certain additional modifications are found to decrease immunogenicity and enhance translation*". [JA/8/340] [SUPP/2/87]

70. As for the finding that Example 31 is "*open ended*" (see also §321(iii)), this is also an error. The Judge focused in §321(iii) on the use of "*include e.g.*" before the list of modifications in [00291] but, when read in the context of UPenn as a whole, the skilled reader would appreciate that the [00291] list corresponds to the modified nucleosides listed in the three lists in the body of the document, less those already tested in the Examples (i.e., the [0069] list). They would not read "*include e.g."* as suggesting that any wider pool of nucleosides should be considered.[4] [CORE/5/116] [SUPP/2/160]

71. Second, the Judge found at §325 that m1Ψ is not "*an individualised disclosure*" in [00291]. This seemed principally to be based on the fact that it is one of 96 nucleosides in [00291]. [CORE/5/117]

[4] Which they would not be, since the 96 listed represent the modifications listed in the RNAMD at the time, again less the ones tested in UPenn (Enright 1 §§7.19 & 7.81). [SUPP/9/224 & 225]

72. We have addressed the law on "*individualised descriptions*" above. The question is partly one of degree. The Judge was right to find that there is no fixed numerical cut-off for individualisation (§131), and the context of the disclosure will be relevant. [CORE/5/78]

73. Just as in *Almirall* where the compounds of the 159 Examples were individually described, in Example 31, [00291] individually describes and therefore discloses each of the 96 listed nucleosides. The Judge gave no reasons in §325 as to why he found to the contrary. [CORE/5/117]

74. The Judge also relied in this context on his finding that the [00291] list was open ended, which we have addressed above.

75. The Judge was wrong to find in §326 that if m1Ψ *was* individually described (and therefore disclosed) in Example 31 then there was additionally a need for a "*statement of preference*" for it. In any event, the [0056] nucleosides (including m1Ψ) would be preferred for the reasons explained at paragraphs 21 to 31 above. [CORE/5/117]

76. Since m1Ψ is individually described in [00291] and the correct construction of Example 31 is that it teaches the skilled reader to go back and perform Example 2 with all of the RNAs it discloses, this inevitably involves synthesis of RNA-1866, an mRNA with a polyA tail where 100% of the Us are replaced by m1Ψs. Claims 3 and 5 are thus not novel under Route 1. [SUPP/2/161]

77. If we are wrong and one must select either an mRNA (to hit claim 3) or specifically an mRNA with a polyA tail i.e., RNA-1866 (to hit claim 5 as well) from Example 2, the Judge was wrong to find that there are not sufficient pointers in either case, such that the combination is disclosed.

78. mRNAs are RNAs that are translated; UPenn is a document focused on modifications to RNA to reduce immunogenicity *and enhance translation*. Testing the effect on translation is also expressly said to be one of the objectives of Example 31 (see above). The Judge made a finding to that effect in §377, also finding that the skilled person would think translation was of importance given the advance of UPenn over the CGK in that area. Claim 1 of UPenn claims an mRNA, and claim 2 adds the requirement for a polyA tail. The same pointers to a polyA tail based on the CGK and Example 12 as relied on in relation to Route 3 above also apply. Claims 3 and 5 are not novel under Route 2. [CORE/5/126] [SUPP/2/142-143]

OBVIOUSNESS (GROUNDS 1-3 (SKILLED PERSON) AND 7-9 (OBVIOUSNESS))[5]

79. Pfizer/BioNTech recognise the challenge inherent in overcoming a finding of (non)-obviousness on appeal. However, on this occasion it is clear that the Judge fell into error in characterising the skilled person and thereby erred in his assessment of the evidence. This resulted in him imposing his own erroneous conclusion as to inventive step, when the correct approach would have been to find the invention obvious. We address below obviousness over UPenn. Ground 10 – obviousness over Karikó 2008 – is no longer pursued on this appeal.

The law of obviousness

80. The proper approach to obviousness is as set out by the Supreme Court in *Actavis v ICOS* [2019] 1 All ER 213 at [52]-[73]. In [63] the Court referred to the oft-cited passage of the judgment of Kitchin J in *Generics v Lundbeck* [2007] RPC 32 at [72]. [JA/14/635-643] [JA/14/639]

81. One consideration that may apply in a given case is whether something is obvious to try with a fair or reasonable expectation of success. In *MedImmune v Novartis* [2013] RPC 27, Kitchin LJ held at [91] (cited with approval by the Supreme Court in *ICOS* at [65]): [JA/10/448-449] [JA/14/639-640]

> 91. …Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way.

82. As the Supreme Court also observed in [65], there is no requirement that it is manifest that a test ought to work, since that would impose a straitjacket which would preclude a finding of obviousness in a case where the results of an entirely routine test are unpredictable. Some experiments which are undertaken without any particular expectation as to result are obvious. See also the "Try and see situation" EPO jurisprudence in the *Case Law of the Boards of Appeal of the European Patent Office*, 10th edition, I.D.7.2. [JA/14/639-640] [JA/23/909-911]

[5] See also Ground 4 (construction of [0056] of UPenn), discussed under Novelty above. [CORE/2/30]

83. Consideration may also be given as to whether the skilled person has a motivation to take a particular step (see *ICOS* [70]). However, the absence of a particular motive to take a particular step is not fatal to an obviousness attack – see Floyd J in *Research In Motion UK Ltd v Visto Corp* [2008] Bus LR D89 at [73], citing this Court's judgment in *Pharmacia v Merck* [2002] RPC 41. [JA/14/641] [JA/6/245]

84. Where these considerations do apply in a given case, they are no more than aspects of the statutory question – was the invention obvious? – and they should not be permitted to "*take on lives of their own*": see Lewison LJ in *MedImmune* at [181]-[182]. [JA/10/464-465]

The Judge's findings on obviousness

85. The Judge considered obviousness from §358. He correctly found that: [CORE/5/123]

(a) The scientists behind UPenn were of the highest quality and eminence in the field (§§292 & 370); [CORE/5/109 & 125]

(b) The data on Ψ were very promising and of real interest (§§360(i) & 361); [CORE/5/123-124]

(c) The skilled person would not understand from UPenn the reason why Ψ performed so well (§§366 & 382); [CORE/5/124 &127-128]

(d) Example 31 is *"a positive teaching to look for other, better, nucleosides, which is a technical teaching*" (§379(v)); [CORE/5/127]

(e) It would be possible to make m1Ψ-modified mRNA if m1Ψ were selected (§§360(iv) & 362); and [CORE/5/124]

(f) If the skilled person made m1Ψ-modified mRNA, the most obvious thing to do would be to modify 100% of the Us and to include a polyA tail (§§360(v) & 362). [CORE/5/124]

86. Despite these findings, the Judge found that EP949 was not obvious over UPenn (§415). Central to the Judge's reasoning, however, were the following errors of principle (which overlap and which each feed into the overall analysis): [CORE/5/133-134]

(a) **Skilled person**: An incorrect identification of the skilled person and the associated finding that Prof Rosenecker was a more useful witness in helping the Judge to understand how the skilled person would think than Dr Enright;

(b) **[0056]**: An erroneous construction of [0056] as not being a technical teaching of a list of Ψ-like nucleosides of particular interest;

(c) **Hindsight**: A finding that Dr Enright's conclusions as to obviousness were given with hindsight, which was wrong and unfair;

(d) **Expectation of success**: An unwarranted overemphasis on the skilled person's expectation of success when testing additional modified nucleosides, and misapplication of *ICOS v Actavis*.

87. Had he not made any or all of the above errors, the Judge would have found that EP949 was obvious over UPenn, as we explain below.

The skilled person

88. The Judge correctly identified that the characterisation of the skilled person was important and underpinned the right approach to obviousness (§266). His errors in respect of the skilled person therefore undermine his overall conclusions on inventive step. [CORE/5/104]

89. It was common ground at trial that the problem that EP949 aims to solve is the problem of increasing the translation and reducing the immunogenicity of mRNA (§§257-258). [CORE/5/102]

90. The fact that the claims (and indeed the specification) of EP949 are not limited to any particular use of the mRNA, and in particular are not limited to use of the mRNA in therapy, was something that the Judge correctly took into account when rejecting Moderna's narrow definition of the skilled person, which was limited to a team working on developing mRNA for the purposes of "transcript therapy" (§261). [CORE/5/103]

91. Rather, the Judge (again, correctly) found that there were real teams working in a wide range of fields where a solution to the problem aimed to be solved by EP949 could be useful – see §260(i)-(ix) (line spacing removed): [CORE/5/103]

> i) Cellular reprogramming studies; ii) Immunotherapy; iii) Direct vaccination; iv) Studying gene expression and the efficacy of RNA platforms; v) Studying mechanisms of translation and immune response; vi) Studies on zinc finger nuclease technology; vii) Neuroscience research; viii) Developmental research; and ix) Gene (or protein) replacement therapy.

92. The Judge went on to find that the skilled person was someone with knowledge of RNA biology, with a practical interest in improving the use of mRNA in relation to translation and immunogenicity in any of those sub-fields (§263). [CORE/5/103]

93. The Judge then fell into error. He found that the skilled person would not have an interest in fundamental research (§§259 & 266) and that Pfizer/BioNTech's expert, Dr Enright, was not from any of the sub-fields identified in his list but was *"a pure, basic scientist"* (§265). [CORE/5/102 & 103] [CORE/5/103-104]

94. Both of these findings are wrong and difficult to reconcile with the §260 list. Further, the relevance of Dr Enright's personal experience is questionable in any event (see *Rockwater v Coflexip* [2004] RPC 46 at [12]). [CORE/5/103] [JA/4/172-173]

95. As the Judge explained in §260, this list was compiled based on what Pfizer/BioNTech had established in cross-examination by reference to a large volume of literature from a large number of real-life groups working in these various sub-fields. [CORE/5/102-103]

96. The Judge did not descend into the details of the work in the Judgment – expressly stating at §260 that he considered he need not. However, examination of some of the details illustrates the Judge's error(s). [CORE/5/102-103]

97. First, we note that there is no bright dividing line between what might be considered "fundamental research" and "therapeutic research". Dr Enright explained in his evidence (undisputed by Prof Rosenecker and unchallenged by Moderna) that the boundary between 'downstream' therapeutic applications and more fundamental 'upstream' research investigations "*is somewhat artificial*" (Enright 2 §2.7). [SUPP/14/248]

98. Either way, the Judge's apparent exclusion of "*fundamental research*" and rejection of Pfizer/BioNTech's position on the skilled person is internally inconsistent with his §260 list, since the list includes a number of fundamental research fields. [CORE/5/103]

99. The §260 list is broad. It includes fields plainly towards the therapeutic end of the spectrum, such as direct vaccination (item (iii)). But it also includes fields towards the fundamental end of the spectrum, such as studying gene expression and the efficacy of RNA platforms (item (iv)), studying mechanisms of translation and immune response (item (v)), and neuroscience and developmental research (items (vii) and (viii)).

100. Regarding sub-field (iv), it was established that one real-world team working in this area was Dr Enright's group, which used mRNA encoding reporter proteins to analyse

microRNA binding in zebrafish.[6] It was also established that work from the Karikó/Weissman group, including the Karikó 2008 prior art which used mRNA encoding reporter proteins to assess the effects of nucleoside modifications on translation, fell into this category.

101. We note that this description also applies to the work in EP949, which similarly used mRNA encoding reporter proteins to assess the effects of nucleoside modifications on translation (*in vitro*).

102. The main focus of Dr Enright's research over the years has been on microRNAs, which are short non-coding RNAs that bind to mRNAs and regulate their stability and translation (§§180-181). His work has therefore necessarily involved not only a deep understanding of mRNA biology but also practical experience of working with mRNA in various experimental systems, one example of which was the zebrafish work referred to above. [CORE/5/89-90]

103. The Judge therefore unfairly and wrongly pigeon-holed Dr Enright as being a "*pure, basic scientist*" (§265) whose work was "*at the more theoretical end of the spectrum*" (§51). His own work was an example of one of the sub-fields in which the Judge found a solution to the problem solved by EP949 would be useful i.e., that defined the skilled person. [CORE/5/103-104] [CORE/5/58]

104. The Judge emphasised in §266 that the skilled person must have a "*practical interest*" in the application of the invention. This is correct, but this is not incompatible with the appropriate skilled person encompassing someone working on fundamental research. Indeed, the Judge found at §261 that the teams working in all the §260 sub-fields were "*looking for practical results*" – this therefore included Dr Enright's zebrafish work, and Karikó's 2008 work. [CORE/5/104] [CORE/5/103]

105. This is all consistent with the well-established principle that a patent is addressed to those likely to have a real and practical interest in the subject matter of the invention, which includes making (or devising) it as well as putting it into practice: see Henry Carr J in *Garmin v Koninklijke Philips* [2019] EWHC 107 (Ch) at [85(i)] and Birss J in *Illumina v Latvia MGI* [2021] RPC 12 at [58]. [JA/13/566] [JA/13/680-681]

[6] Giraldez *et al*. [SUPP/4]

106. Further, a practical interest (or practical goal) is not synonymous with a therapeutic application. A contribution to the study of, say, gene expression and the efficacy of RNA platforms (item (iv)) or the mechanisms of translation and immune response ((item (v)) is a practical goal. Indeed, these better align with the claimed technical contribution of EP949, which simply makes and tests a selection of modified nucleosides, including m1Ψ.

107. Neither expert could speak from the perspective of a scientist in all of the §260 sub-fields. The Judge rightly found at §265 that no individual could. There was therefore no basis upon which he could find that evidence given from the perspective of an expert from one sub-field could be of more or less assistance than one from another sub-field. This is because it is well-established that if the invention is obvious to a skilled person from *any* of the identified sub-fields, then it is invalid (a point the Judge made in §265). [CORE/5/103-104]

[0056] and hindsight

108. Errors (b) and (c) (see paragraph 86 above) centre on the Judge's conclusion at §415 that Pfizer/BioNTech's *"focus on [0056] is artificial and hindsight-driven"*. The Judge found at §62 that Dr Enright's heavy focus on [0056] would be unlikely without hindsight. This was also affected by error (a) on the skilled person. [CORE/5/133-134] [CORE/5/60]

109. As explained above, had the Judge properly construed [0056] of UPenn, he would have found that it was presenting a list of Ψ-like nucleosides of particular interest as a technical teaching. Had he done so, he would not have gone on to find that there was anything artificial or hindsight-driven about a focus on [0056].

110. The Judge went further on hindsight as regards Dr Enright, wrongly and unfairly holding at §63 that his conclusions on obviousness more generally were given with hindsight. This was a material reason why the Judge found that Prof Rosenecker was a more useful witness to him (§66). [CORE/5/60] [CORE/5/60]

111. We have already explained why the Judge wrongly labelled Dr Enright as not being in the relevant field at the priority date. Moreover, Dr Enright's evidence was prepared in line with the general "sequential unmasking" practice adopted in patent cases to protect experts against the risk of hindsight. He also explained that before he was shown EP949 he did not know that m1Ψ was used in the Covid-19 vaccines (Enright 1 §§3.4-3.5). As the Judge accepted, Moderna did not challenge this at trial (§54). [SUPP/9/218-219] [CORE/5/59]

This is the ultimate hindsight which should be avoided in patent cases, and which was avoided here.

112. Nevertheless, the Judge went on to find that "*there was some material hindsight in Dr Enright's approach overall*" (§63(ii)). This is deeply unfair and wrong. [CORE/5/60]

113. In particular, at §§56-60 the Judge relied in support of his hindsight finding on §7.16 of Dr Enright's first report, where in addressing [0056] of UPenn Dr Enright stated that the skilled person *"would note that while m^5D is not literally a Ψ derivative like the others in the group, it does share structural similarities with the others, in particular m1Ψ, which would explain its inclusion"* in [0056]. [CORE/5/59] [SUPP/9/223]

114. It was common ground between the experts that m5D is not a pseudouridine. Nevertheless, [0056] includes m5D as a "pseudouridine". The skilled person would wonder why. The above was Dr Enright's view as to what they would think.

115. What Dr Enright said is factually correct. m5D *is* most structurally similar to m1Ψ of the [0056] nucleosides – see the structures of the [0056] molecules depicted at §306; the methyl (CH_3) group is present at the same position on m5D and m1Ψ. Prof Rosenecker agreed (T4/511_{11}-512_{12}). That is all Dr Enright was saying. [CORE/5/114] [SUPP/18/285-286]

116. The fact that there existed other nucleosides *not* mentioned in [0056] that are more structurally similar to other members of [0056] than m5D is to m1Ψ, to which the Judge referred in §60, is irrelevant. That was not what Dr Enright was addressing, which was why the skilled person would think the particular non-pseudouridine m5D had been included in a list otherwise populated by pseudouridines. [CORE/5/59-60]

117. It was therefore wrong and unfair of the Judge to find that this aspect of Dr Enright's evidence was indicative of a particular focus on m1Ψ on the part of Dr Enright that fed into his obviousness analysis (§60). This is particularly so when Dr Enright's evidence was <u>not</u> that the skilled person would want to test m1Ψ and only m1Ψ – his evidence was that they would want to test all five of the [0056] modifications. Further, Moderna did not challenge that Dr Enright gave his views on the prior art and obviousness before being aware the case was anything to do with m1Ψ. [CORE/5/59-60]

Expectation of success

118. The above errors fed into the ultimate conclusions reached by the Judge on obviousness.

119. Either as a result of wrongly characterising the skilled person, or of wrongly finding that Dr Enright was guilty of hindsight, the Judge was wrong to hold that Prof Rosenecker was a more useful witness than Dr Enright in helping to understand how the skilled person would think and reason at the priority date (§66). Putting aside the irrelevance of the question of which expert most resembles the notional skilled person (per *Rockwater*), Dr Enright's evidence was given from the perspective of the correct expert in the field. [CORE/5/60]

120. In particular, had the Judge not made these errors, he would have accepted Dr Enright's evidence, supported by clear and cogent reasons and undisturbed by cross-examination, that it would be obvious to the skilled person to explore other modified nucleosides, that they would start by examining modifications similar to Ψ and that the skilled person would want to test all five of them, including m1Ψ (Enright 1 §§6.48-6.55 & 7.84-7.87; T2/186$_{19}$-187$_{25}$, T2/200$_{10-20}$, T2/227$_{3-24}$, T2/294$_{3-16}$, T2/299$_{10}$-301$_{13}$). We pick up on further points of detail of Dr Enright's evidence in context below. [SUPP/9/220-222] [SUPP/9/226-227] [SUPP/16/259-260] [SUPP/16/262] [SUPP/16/264] [SUPP/16/269] [SUPP/16/270]

121. The Judge's errors on the skilled person also impinged on his approach to motivation and expectation of success.

122. As noted above, it was common ground that the skilled person would not understand from UPenn the reason why Ψ performed so well (§§366 & 382). The Judge heavily relied upon this being a reason why the skilled person would <u>not</u> seek to test other modifications, because any such choice would be made "blind" and without any concrete expectation of success (§§266, 362 & 382). [CORE/5/124 & 127-128] [CORE/5/104,124 & 127-128]

123. Dr Enright's evidence was that the skilled person would not assume that the results seen with Ψ in UPenn would necessarily be the best that could be obtained and would be interested in exploring alternative modifications to see whether any additional or similar benefit could be obtained (Enright 1 §7.84; T2/227$_{3-24}$ & 299$_{10}$-301$_{13}$). Importantly, such additional or similar benefits would be useful in all of the sub-fields embodying the skilled person (i.e. the §260 list). Indeed, Prof Rosenecker agreed in XX that having alternative modifications would be valuable for his work at the more therapeutic end of the spectrum i.e. in "*the clinic*" (T4/534$_{18-20}$). It goes without saying that better performing modifications would also be useful. [SUPP/9/226; SUPP/16/264 & 270] [CORE/5/102-103] [SUPP/18/291]

124. We pause to note that the *idea* of testing additional modifications is not one that the skilled person would need to come up with themselves; it is expressly suggested to

them by Example 31 of UPenn, which, as the Judge found, is *"a positive teaching to look for other, better, nucleosides"* (§379(v)). [CORE/5/127]

125. Further, given that this was a nascent field and that the prior art represented an important advance over the CGK (§377) and addressed a primary problem in the field – increasing translation – Prof Rosenecker accepted in XX that there was room for optimisation of the work in the prior art (T4/519$_{9\text{-}13}$). Indeed, as a matter of reality Prof Rosenecker's group sought to optimise Karikó's 2005 work by trying different modifications to Ψ and by adjusting the % modifications – see the Kormann 2011 work summarised at §§252-254. [CORE/5/126] [SUPP/18/287] [SUPP/5] [CORE/5/101]

126. However, Dr Enright explained that the skilled person would have an additional or alternative motivation to test the Ψ-like modifications, namely to find out why Ψ worked as well as it did – see T2/181$_{10\text{-}24}$ and T2/200$_{10\text{-}20}$. Prof Rosenecker agreed in XX that, for a fundamental scientist, one way of testing why Ψ worked so well would be to make small alterations to Ψ to see if the effect was nullified or maintained – see T3/439$_{5\text{-}19}$, T3/443$_{25}$-444$_{15}$ and T4/533$_{19}$-534$_{20}$. [SUPP/16/258 & 262] [SUPP/17/274 & 275] [SUPP/18/291]

127. The Judge sought to characterise work driven by this motivation as being work "*without any practical goal in mind*" (§266). But this is wrong for the reasons given above – a practical goal does not require a therapeutic application but encompasses scientists looking for any practical i.e. useful results across the scope of the fields listed in §260. Further, the contribution of the patent is limited to an alternative to Ψ, which the Judge correctly recognised but then appeared to ignore in his obviousness analysis. [CORE/5/104] [CORE/5/102-103]

128. In any event, upstream fundamental research underpins and feeds into downstream therapeutic research, such that they could be said ultimately to share the same practical goals, differing only in the immediacy with which that goal might be realised. As Dr Enright explained, although his work was further upstream from the clinic than Prof Rosenecker's, like most scientific research its purpose was still ultimately to provide therapeutic benefit (T1/125$_{25}$-130$_{16}$). [SUPP/15/256-257]

129. This additional or alternative motivation also feeds into the significance of the Charette & Gray review article considered by the Judge at §§385-402. The Judge found that the skilled person, had they consulted the RNAMD, would read Charette & Gray as it was given as a reference for Ψ. The evidence of both experts was that [CORE/5/128-131]

they would do this because they had no understanding as to why Ψ worked better than U (§§386-387). [CORE/5/128]

130. The Judge then made findings as to what the skilled person would learn from Charette & Gray from §390, ultimately finding in §400 that it endorsed a particular theory – the hydrogen bonding theory – that, if applied to m1Ψ, would tend to suggest reduced stability. The theory was that the N1 hydrogen in Ψ, by reason of its H bonding capability, was responsible for Ψ's improved performance. m1Ψ contains a methyl (CH_3) group at that N1 position, thereby removing that H bonding capability. [CORE/5/129]

131. The Judge correctly found that the skilled person would not think that this was a theory that was supported by strong evidence, or was the only theory, and that its application to mRNA was a matter of uncertainty (§400). [CORE/5/131-132]

132. Had the Judge correctly identified the skilled person and/or not disregarded Dr Enright's evidence in favour of Prof Rosenecker's as he did (§66), he would have found that, faced with this theory and the doubt(s) it might cast about m1Ψ as a result, the way to resolve it would be to test m1Ψ i.e. to remove that hydrogen bonding capability and observe the effect. The Judge was wrong to find to the contrary in §402. Indeed, it was Prof Rosenecker who agreed that the only way to test the Charette & Gray theory would be to test m1Ψ[7] – see $T4/507_2$-508_2. [CORE/5/60] [SUPP/18/284-285]

133. The Judge further erred in placing too much weight on expectation of success as a factor in his assessment of obviousness – see §§409, 415 & 416. [CORE/5/132, 133-134]

134. Claim 3 is to an mRNA as such, and the technical contribution of EP949 is no more than the provision of m1Ψ-modified mRNA as an alternative to Ψ-modified mRNA (§§421-422). Lewison LJ was clear in *MedImmune* that there is one statutory question: was the invention obvious at the priority date? Accordingly, the Judge should have simply asked himself the question: did it require invention at the priority date to make mRNA in which the Us were replaced with m1Ψs? [CORE/5/135]

135. Instead, the Judge overly focused on the expectation of success, wrongly allowing this consideration to override the statutory question.

[7] Contrary to the Judge's §402, Prof Rosenecker thus went further than conceding only that it would be possible to test. [CORE/5/131]

136. Dr Enright's evidence was that the skilled person would have wanted to test all the Ψ-like modifications in the short [0056] list of UPenn (Enright 1 §§6.50-6.51). They would be most optimistic about modifications which represented small incremental changes to Ψ and less optimistic about modifications which were modified on the Watson-Crick face (Enright 1 §§6.51-6.53). [SUPP/9/221] [SUPP/9/221-222]

137. In advance of carrying out the experiments, the skilled person would expect that some modifications might be worse, some might be as good as, or some might be better than Ψ. There is no invention in taking up the invitation of Example 31 to test further modifications and carrying out those routine experiments on the handful of [0056] nucleosides to ascertain which fall into which category. That proposition still holds true even if, because of the nature of the field, the skilled person cannot predict in advance which the "as good as" or "better" ones might be. The field is empirical.

138. The Judge was therefore wrong to find that there was any inconsistency in Dr Enright's evidence that he would test all five of the [0056] modifications yet would prioritise some over others (§384), or that his *"willingness to entertain modifications which could produce negative ("catastrophic") results"* was somehow unrepresentative of the skilled person (§§50(iv)-51 & 66). As Dr Enright explained, *"science is certainly very unpredictable, but again part of the scientific process is to test things, to have hypotheses and assumptions beforehand and then to do experiments to see which of those pan out in reality, and that is how we learn and improve"* (T2/213$_{2\text{-}6}$). [CORE/5/128] [CORE/5/58 & 60] [SUPP/16/263]

139. If the law imposed a requirement that the skilled person should always be able to predict in advance which tests will be successful, this would lead to patents being granted too freely in empirical fields. This is exactly the danger Lord Hodge identified in [65] of *ICOS*, and the Judge was wrong to limit the application of that proposition to situations in which it is expected that a routine experiment will yield a positive result (§417). It also applies to empirical fields. [JA/14/639-640] [CORE/5/134]

140. Further, as explained above, "success" in the present case does not equate to finding a modification that is better than Ψ. An alternative to Ψ would equally be deemed to be "success"; indeed, that is the claimed technical contribution of EP949. This was also the view of both experts (see above). In fact, insofar as the skilled person's motivation was to try to understand why Ψ performed well, discovering that a modification performed worse than Ψ could be valuable information – see T2/188$_{17\text{-}$ [SUPP/16/260]

$_{25}$ & 189$_{9}$-190$_{7}$. The Judge was therefore wrong to find at §380 that Pfizer/BioNTech's case involved the unspoken assumption that there would be modifications better or as good as Ψ among the ones the skilled person would test; its case was the exact opposite: one does not know until one tries. [CORE/5/2127]

141. At [91] of *MedImmune*, Kitchin LJ stated that whether a step has a reasonable prospect of success depends on all the circumstances, including: [JA/10/448-449]

(a) The ability rationally to predict a successful outcome – this is not possible in this field (see above);

(b) The extent to which the field is unexplored – it was common ground that the prior art was the first piece of work showing increased levels of translation using modified nucleosides (Rosenecker 1 §235; T4/518$_{21-25}$) and, as such, Prof Rosenecker agreed there was *"room for optimisation*" (see above). The field was also unexplored to the extent that the skilled person would not know why Ψ works as well as it did; and [SUPP/6/210] [SUPP/18/287]

(c) The complexity or otherwise of the experiments, and whether the experiments can be performed by routine means – the Judge accepted that the experiment formats proposed would be routine (§418). [CORE/5/134]

142. The Judge should have found that "expectation of success" in the present case should be afforded considerably less weight, if any at all, when weighed in the balance against the other considerations.

143. As such, the Judge should have found that the claimed mRNAs of EP949 were not inventive over UPenn. It would be obvious to the skilled person within any of the fields identified in §260 to follow the teaching of Example 31 to test other nucleosides, and they would test the [0056] list of Ψ-like modifications of particular interest. They would have sufficient motivation either to find modifications that were as good as or better than Ψ in this unexplored field, alternatively to find out why Ψ worked as well as it did by making small changes to Ψ and observing the effect. They would thus synthesise using routine methods an mRNA with a polyA tail where 100% of the Us were replaced with m1Ψs. [CORE/5/102-103]