Appeal Nos. CA-2024-0023525 & 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

MODERNA'S SKELETON ARGUMENT IN RESPONSE TO THE APPEAL

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INTRODUCTION

1. References (§) below are to paragraphs of the Judgment. References in bold (**paragraph x**) are to paragraphs of Pfizer/BioNTech's (**PBNT's**) skeleton argument.

2. For the purposes of this appeal, only claim 3 of EP949 needs to be considered.[1] Claim 3 is for:

> "An mRNA wherein 100% of nucleotides comprising uracil in the mRNA are relaced with nucleotides comprising N1-methyl-pseudouridine."

3. Claim 3 combines three features:

   (1) A particular type of RNA, namely *messenger RNA* (abbreviated as mRNA). Cells produce several types of RNA, of which mRNA is the only one whose function is to encode proteins. This is achieved by converting the sequence of nucleotides in the mRNA molecule into the corresponding chain of amino acids which constitutes the protein in question – a process known as "translation" (§§192-195).

   (2) Which comprises a particular modified nucleoside – *N1-methyl-pseudouridine* (**$m^1\Psi$**).

   (3) And in which *100%* of the uridine nucleotides are replaced with $m^1\Psi$.

4. The prior art (**UPenn**) is a lengthy patent application, comprising 291 paragraphs of text, the bulk of which concerns experimental work on six modified nucleosides (m^5C, m^5U, m^6A, s^2U, Ψ, and Um) including the methods used, the results and the conclusions to be derived therefrom (Examples 1-16). Examples 17-31 are prophetic i.e. without data and yet to be performed.

5. The experiments in Examples 1-16 were conducted *in vitro,* in cultured cells and *in vivo* but the only modification taken forward into the *in vivo* work was Ψ (pseudouridine) (§303). The key message of UPenn about these experiments is contained in [00241] and [00244] – [00246] which highlight the advantages of Ψ in three respects – enhanced translation, increased stability and reduced immunogenicity. (§304)

6. UPenn does not say, nor would it be possible to work out, why Ψ had worked so well (§382). Nevertheless, the skilled person would see the data on Ψ as very promising and of real interest (§§360-361).

[1] Claim 5 not being the subject of any of Moderna's requests pending before the EPO.

7. UPenn lists 96 further modified nucleosides by name (including $m^1\Psi$) but presents no experimental results for any of them. Also listed are many different types of RNA (including, amongst others mRNA, dsRNA, siRNA and shRNA) and a wide range of percentage modifications (<0.1% to 100%) for any given natural nucleoside.

8. **Novelty**: For a claim to be anticipated, its subject-matter must be "*directly and unambiguously derivable*" from the prior art; alternatively the prior art must contain "*clear and unmistakable directions*" to do what the patentee claims to have invented.

9. In respect of each Route advanced by PBNT, the Judge made findings as to how the constituent disclosures in UPenn would be understood by the skilled person. Those findings were made with the benefit of evidence from the experts (Dr Enright on behalf of PBNT and Professor Rosenecker on behalf of Moderna), both of whom considered the disclosure of UPenn at length and were cross-examined on the same.

10. The Judge's task was to evaluate UPenn in the light of that evidence and arrive at a judicial determination as to whether it disclosed the combination of all the features in claim 3 either directly and unambiguously or by way of clear and unmistakable directions. He rightly concluded that claim 3 was not anticipated.

11. **Obviousness:** The Judge adopted the right approach in law. He undertook a careful and detailed appraisal of the evidence, in the light of which he correctly identified EP949's skilled person, correctly found that Dr Enright's approach was tainted by hindsight, and rightly concluded that the invention of claim 3 was not obvious. As the Judge explained in §415:

> "I must assess all these matters in the round. Doing so, I find that Pfizer/BioNTech's obviousness case fails, *and it is not a close call, either*." (emphasis added)

12. In relation to technical contribution (**paragraph 7**), the Judge summarised the experimental work in EP949 at §§279-284. He did not have to decide whether the results demonstrated that $m^1\Psi$ is superior to Ψ because Moderna accepted (for the purpose of these proceedings) that EP949's technical contribution is the provision of $m^1\Psi$ as alternative modified nucleoside to Ψ. The Judge rightly found that the obviousness case still failed – his findings in relation to the skilled person, expectation of success, unpredictability and so on applied even if the skilled person was looking for alternatives to Ψ rather than improvements on it. (§422)

13. In **paragraph 10**, PBNT seeks to re-argue obviousness on the basis 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 to identify an alternative to Ψ*" But that is precisely the submission that the Judge rejected in §415 where he found that UPenn contains no special pointer try other pseudouridine modifications and "*the focus on [0056] is artificial and hindsight-driven*".

NOVELTY OVER UPENN (GROUNDS 4, 5 & 6)

THE LAW OF NOVELTY

14. We do not detect any relevant criticism by PBNT of the Judge's account of the law at §§121-146 save in relation to independent lists at §145, which we address below in the context of Route 3. For present purposes, we draw attention to the following principles, all of which we understand to be agreed.

15. **The basic tests:** As indicated above, the disclosure test requires that the claimed subject-matter is directly and unambiguously derivable from the prior art. Alternatively the prior art must contain clear and unmistakable directions to do what the patentee claims to have invented. These are both aspects of a single principle – anticipation requires prior disclosure of subject-matter which, if performed, must necessarily infringe the patented invention (*Synthon v SmithKline Beecham Plc (No.2)* [2006] 1 All ER 685 at [22]-[24]). (§§122-125)

16. The whole prior art document has to be considered, but that does not mean that it is a reservoir from any part of which a feature can be combined with a feature from some other part, in the absence of a clear teaching to do so. (§126)

17. **Individualised description:** This concept provides a tool for assessing whether the claimed subject-matter is directly and unambiguously derivable from the prior art. The question is one of degree and the specificity of any indicated purpose can be relevant. (§129)

18. There is no conceptual difference between a list and the identification of a group such as a Markush formula (§129). For a case in which the individualised disclosure test was applied to a list of named compounds, see *GSK v Wyeth* [2016] EWHA 1045 (Ch) at [157]-[168].

19. **Selection from multiple lists:** The selection of features from separate lists is not formalistic in the sense that a choice from two lists automatically means that such subject-

matter is not individualised. The ultimate question is still clear and unambiguous disclosure. (§136)

20. **Pointers:** A particularly common form of pointer is a statement of preference within a list. In a number of the EPO cases, it has been held that there was added matter in combining a preferred member of one list with a member of another list for which no preference was expressed. In general, what the EPO looks for is a pointer to the claimed combination, although this is not an absolute rule (§139). Pointers are a facet of deciding the question of clear and unambiguous disclosure and not a licence for holding something to be disclosed, merely because it was an obvious choice. (§146)

ROUTE 3

21. This Route depends on [004], [0056], [0074], Example 2 and Example 7 of UPenn. Claim 1 is advanced as an alternative to [004].

22. PBNT's skeleton includes a number of arguments which were not foreshadowed in the Grounds of Appeal. We have neverethless addressed the new arguments below.

23. We begin with a brief account of the genesis of Route 3. PBNT's skeleton argument for the trial made no mention of this Route – anticipation was advanced solely on the basis of Route 1. In oral opening, Counsel introduced the first iteration of what eventually became Route 3 as PBNT's secondary case. However at that stage, no reliance was placed on any of the Examples and [006] was identified as the principal starting point [T1/p41-p46/23]. This version of Route 3 was maintained in PBNT's written closings, albeit with [004] and [006] now placed on an equal footing. It was only after the Judge asked for further submissions on novelty in chart form that the final version of Route 3 (now including Examples 2 and 7 and claim 1) appeared.

24. We do not suggest that this chronology rules out Route 3. However, the test for anticipation is one of direct and unambiguous disclosure or clear and unmistakable directions, in either case without knowledge of the subsequent patent (*Synthon* at [23]). The late emergence of Route 3 and its evolution during the course of the trial are powerful indications that it is a hindsight-driven construct.

25. In any event, the Judge's reasons for dismissing anticipation by Route 3 are faultless. PBNT contended that [0056] presents a preferred list of Ψ-like modifications. The Judge rejected that case (§335) and went on assess whether Route 3 involves a permissible selection of features from two lists, namely the list of modified mRNAs comprised of

[004]/claim 1 read together with [0056] and the list of percentage modifications in [0074]. That approach was soundly based in law (see §§132-144).

26. The Judge rightly found that: (1) m1Ψ is not said to be preferred and (2) UPenn does not disclose a preference for 100% replacement (§§336-338). The Judge could have stopped there – the constituent elements of Route 3 do not directly and unambiguously disclose an mRNA comprising 100% m1Ψ, nor do they provide clear and unmistakable directions to make the same.

27. However, the Judge went further and analysed Route 3 on the assumption that UPenn *does* include a pointer to 100% replacement (i.e. contrary to (2) above). In §339, he concluded that there was still no anticipation because UPenn contains no pointer to the *combination* of m1Ψ and 100% replacement and Route 3 requires combining something assumed to be preferred (100%) with something in an unclear and apparently open-ended list (m1Ψ). Again the Judge's approach was soundly based in law (see §139).

28. PBNT's last throw of the dice before the Judge was to submit that the choice from the list of percentage replacements in [0074] is not independent of the choice of modified nucleoside in [0056]. The Judge rightly rejected that submission (§145).

29. With that introduction, we turn to the appeal under Route 3. As indicated above, the issue is not whether each feature of claim 3 can be found independently in UPenn, but whether UPenn discloses the combination of claim features to the relevant legal standard. Nevertheless, for ease of reading, we have endeavoured to follow the structure of PBNT's skeleton argument and therefore address Route 3 in the same order, starting with [0056], followed by [004]/claim 1 when read together with [0056] and finally 100% replacement.

Construction of [0056]

30. [0056] is one of 138 paragraphs in the section of UPenn entitled "Detailed Description of the Invention". Each paragraph identifies one or more embodiments of the invention, according to the type of RNA, method of synthesis, modified nucleoside, percentage incorporation, therapeutic target and so on.

31. This section of UPenn includes three lists of modified nucleosides. [0069] identifies the six modifications that were tested. [0070] identifies 92 further modifications, none of which was tested. [0056] defines the term "*pseudouridine*" as referring to the following nucleosides:

    (i) Four derivatives of Ψ, namely $m^1acp^3\Psi$, $m^1\Psi$, Ψm and $m^3\Psi$;

(ii) m^5D (5-methyl-dihydrouridine);

(iii) Ψ ("*a pseudouridine moiety that is not further modified*"), and

(iv) "*any other pseudouridine known in the art*".

32. As with [0070], none of the nucleosides in [0056] was tested in UPenn, other than Ψ. The Judge rightly characterised m^5D as an "*oddity*" since it is not a derivative of pseudouridine (§57).

33. The Judge described [0056] as a "*definition section*" (§335). He was right to do so. [0056] is one of many definition sections in UPenn – also see [0076], [0088], [0089], [00159] and [00167].

34. In this respect, UPenn is unremarkable. Patent specifications often include their own defined terms, typically for the purpose of extending the scope of the monopoly or monopolies claimed. In the case of UPenn, [0056] indicates that those claims in which reference is made to "*a pseudouridine*" encompass not only Ψ but also $m^1acp^3Ψ$, $m^1Ψ$, Ψm, $m^3Ψ$, m^5D and any other pseudouridine known in the art.

35. PBNT contends on appeal (as it did before the Judge) that [0056] would be understood to present a "*preferred list of Ψ-like modified nucleosides*". The Judge rightly rejected that case. Nowhere in UPenn are the nucleosides in [0056] said to be preferred and the promising results with Ψ are irrelevant for the reasons given by the Judge. In particular, the skilled person's reading of [0056] would be informed by the fact that UPenn does not explain, and it would not be possible to work out why, Ψ had worked so well – there could be no inference that the list in [0056] was made on a concrete basis of understanding the mechanisms at work (§382). Furthermore, it was common ground that small structural changes could make a big difference in effect, as exemplified by m^6A which UPenn shows is capable of being transcribed, but the resulting mRNA is not translated (§406). Yet further, the presence of m^5D makes it unclear what thinking had gone into the list (§379(ii)).

36. PBNT's skeleton argument identifies three features of UPenn's disclosure which the Judge is said not to have properly considered in answering the following question – "*Why are these nucleosides specifically called out in [0056]?*" (**paragraphs 28 and 29**). The simple answer to this question is the one given by Professor Rosenecker in the cross-examination quoted at §378 – the skilled person would not know.

37. In any event, the three features identified by PBNT do not lead to its "*preferred list of Ψ-like modified nucleosides"* (**paragraph 29**) for the following reasons:

38. (1) "the very promising data on Ψ": The promising results with Ψ have no bearing on [0056] as discussed above.

39. (2) "the Ψ-like modifications being the only shortlist of nucleosides not tested": [0056] is not a list of a "Ψ-like" modifications because it includes m^5D (see above). Nor is it short because the list extends to "*any other pseudouridine known in the art*" (see below). In any event, the shortness of the list (even if were permissible to exclude any other pseudouridine known in the art) does not constitute disclosure of technical information. That is all the more so when the same compounds appear within the longer list of nucleosides at [00291], in respect of which UPenn contains no experimental results.

40. (3) "the reference in [004] and claim 1 to '*a messenger RNA comprising a pseudouridine residue*'": We address [004] and claim 1 in turn.

41. [004] appears in the section of UPenn entitled "Summary of the Invention". The first paragraph of this section [003] describes the invention in broad terms. It is followed by eighteen paragraphs, each of which describes one or more embodiments of the invention. Certain embodiments relate to RNA generally, whilst others specify a particular type of RNA (mRNA, dsRNA, siRNA, shRNA) as well as oligoribonucleotides and polyribonucleotides. In some embodiments, the modified nucleoside is "*a pseudouridine residue*", in others it is "*a pseudouridine or a modified nucleoside*" or "*m^5C, m^5U, m^6A, s^2U, Ψ, or 2'-O-methyl-U.*" The list includes different methods of production (*in vitro* transcription and *in vitro* synthesis) and also a range of different therapeutic targets. However, nowhere is [004] said to be preferred – it is simply one of many embodiments of the invention, all introduced in the same terms (*"in one embodiment …, in another embodiment …*"). Nor could any preference for [004] be inferred for the reasons discussed above.

42. As for claim 1, it is one of 18 independent claims whose subject matter essentially reflects the list of embodiments described in UPenn's "Summary of the Invention". [004] is not preferred, nor is its corresponding claim 1.

43. In summary, the Judge was plainly right to find that [0056] is not an expression of any technical preference for the listed nucleosides.

44. This finding bears also upon the starting points for Route 3. Whether one starts the analysis with [004] or claim 1, one should not lose sight of the fact that in the absence of any preference for the [0056] nucleosides, there is nothing in UPenn that directs the skilled person to single out [004] or claim 1 from the list of embodiments or claims in which they appear.

[004]/claim 1 read together with [0056]

45. PBNT's skeleton (**paragraphs 36-47**) alleges two distinct errors on the Judge's part, followed by a new argument that m1Ψ is individually disclosed in [0056].

Alleged error #1

46. PBNT contends that 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]*" (**paragraph 38**). PBNT misunderstands the Judge. In §335 he accepts that claim 1 or [004] is at least a legitimate starting point but finds that [0056] does not constitute any technical preference for the listed nucleotides. The Judge is not suggesting that the [0056] nucleosides are therefore not disclosed or cannot be read into claim 1 or [004] (if that was the Judge's view, he would have said so). The Judge is simply addressing (and rejecting) PBNT's case that [0056] presents a preferred list of Ψ-like modified nucleosides.

47. PBNT goes on to submit that if [0056] is rightly characterised as a definition, "*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*" (**paragraph 40**). PBNT has again lost sight of the target for novelty, which is not just m1Ψ or mRNA comprising m1Ψ. The target is the three-part combination of features in claim 3 which includes 100% replacement.

48. If the submission is meant to be directed at the combination of mRNA and m1Ψ, we do not dispute that such a molecule could fall *within the scope* of claim 1 of UPenn. The fact that a given combination falls within the scope of a claim does not however mean that that combination is individually disclosed. Claim 1 also covers mRNAs comprising five other modifications as well as any other pseudouridine known in the art. That is why the Judge rightly went on to consider whether m1Ψ is said by UPenn to be preferred and found that it was not (§336). Had it been, that would have a significant factor in the overall assessment of Route 3.

Alleged error #2

49. The Judge found that that the reference to "*any other pseudouridine known in the art*" in [0056] rendered the list open-ended and unclear (§§335, 339 and 379(iii)).

50. By way of background, modified nucleosides may be either naturally occurring or artificial. As recorded in §203, it was possible to obtain a limited number of modified nucleosides (of both types) from commercial sources. The RNA Modification Database (**RNAMD**) contains information about naturally occurring modified nucleosides. The skilled person

knew that the RNAMD existed and was searchable – they would not know its contents by heart but would know how to access it *when needed* (§250).

51. The Judge was correct to find as he did. Turning to PBNT's criticisms of the Judgment:

52. Enright 1§7.15 (**paragraph 42**). The reliance on Dr Enright is misplaced. Dr Enright's evidence in this paragraph was that the skilled person would be aware that there were no other naturally occurring nucleoside molecules "*by referring to the RNAMD*". In this respect, Dr Enright was saying that it was *obvious* for the skilled person to cross-check the list in [0056] against the RNAMD, as can be seen from Enright 1 §§7.84 -7.85. The result of that exercise forms no part of the disclosure of UPenn, as the Judge rightly found (§335).

53. Use of the RNAMD is "a classic example of the skilled person using their CGK to understand the disclosure" (**paragraph 43**). Again, the submission confuses the issues of disclosure and obviousness – neither expert suggested that the skilled person would need to consult the RNAMD in order to understand [0056].

54. The Judge had no basis to suggest that the skilled person would not know that there were "no [other pseudouridines] in the world" (**paragraph 43**). The finding in question (§335) relates to artificial pseudouridines, as to which the Judge was entitled to find as he did. The existence of artificial nucleosides was CGK (§203) and neither expert suggested that they were thought to exclude derivatives of pseudouridine.

55. The Judge failed to construe UPenn at the date of its publication (**paragraph 44**). The Judge's reference to pseudouridines "*that might be found in the future*" (§335) betrays no such error. As it happens, the Judge's finding reflects precisely the submission that PBNT made in closing ("*Here is a list of pseudouridine-like molecules and any more that might be found*" [T14/p2045/9-13]).

"m1Ψ is individualised in [0056]"

56. The Judgment does not address whether m1Ψ is individualised in [0056] (**paragraph 45**) since this formed no part of PBNT's case at trial. Nevertheless, the findings discussed above dispose of any such argument. [0056] is not a short list – it is open-ended and unclear. Furthermore, UPenn does not specify any purpose for m1Ψ or indeed any of the nucleosides in [0056] other than Ψ.

57. PBNT characterises the finding in §336 as a "*prime illustration of the Judge's improperly strict approach to novelty*" for which he gave no reasons (**paragraph 45**). PBNT is wrong on both counts. In §139, the Judge referred to "*a statement of preference within a list*" as

a particularly common form of pointer. The finding in §336 that "*m1Ψ is not said to be preferred*" is simply the Judge applying that principle to the facts of this case.

58. Finally, PBNT relies on *Almirall v Boehringer* [2009] FSR 12 for the proposition that the prior art may individualise multiple compounds (**paragraph 46**). We do not disagree. However individualisation depends on the facts. In *Almirall*, the prior art disclosed a Markush formula, within which a discrete sub-class of example compounds had been synthesised in the laboratory. The prior art also demonstrated that the relevant compound (aclidinium) had a favourable IC50 in an animal model and showed "real promise" ([217] – [218]). That bears no resemblance to the present case – the class of molecules covered by claim 1 or [004] read together with [0056] is open-ended, none of its members is synthesised and none is preferred other than Ψ.

100% replacement

59. UPenn's "Detailed Description of the Invention" includes four paragraphs that disclose different embodiments of the invention in terms of percentage modification. None of them is tied to any particular type of RNA. [0072] and [0073] relate to the overall percentage of residues that are modified in "*the RNA, oligonucleotide, or polynucleotide molecule*." [0074] and [0075] relate to the percentage of residues of a given nucleotide (uridine, cytidine, guanosine or adenine) that are modified. In [0074] the list of embodiments varies between 0.1 and 100% (33 different embodiments). In [0075], the list varies between <1% and <70% (15 different embodiments).

60. [0072] and [0074] are the only paragraphs in UPenn's general teaching where 100% replacement is disclosed. Notably, 100% replacement is nowhere mentioned in the Summary of the Invention or in any of the claims. However this is not surprising. As discussed below, UPenn teaches that 100% replacement is not always desirable – for some modified nucleosides it has a deleterious effect on translation.

61. At trial, PBNT relied on Example 2, Example 7 and one aspect of the CGK as "pointers" to the 100% embodiment disclosed in [0074]. The Judge rejected this case for the reasons in §§337-339.

62. PBNT's skeleton advances new arguments in relation to 100% replacement that were not advanced before the Judge. We have already described the genesis of Route 3 up to and during the trial. The deployment of these new arguments further illustrates the true nature of Route 3 – a combination of disparate disclosures in UPenn that would never occur to the skilled person without the benefit of hindsight.

63. We deal with the new arguments first before addressing the specific criticisms of the Judgment.

64. "100% replacement would have been assumed" (**paragraph 49**). PBNT says that 100% replacement is the "*default*" in any *in vitro* transcription (IVT) reaction and would have been assumed on reading claim 1/[004]. The flaw in this submission is that there is no teaching in UPenn that the mRNA of claim 1 or [004] must be made by IVT. On the contrary, UPenn includes copious references to coding RNA i.e. mRNA (§176) being made by "*in vitro synthesis*" (see for example [0010]-[0019]). As Professor Rosenecker explained, the skilled person would understand "*in vitro synthesis*" to include non-enzymic methods such as chemical synthesis (Rosenecker 1, ¶146), that is to say other than IVT.

65. 100% replacement is "inevitable" (**paragraph 50**). This submission seeks to side-step [0074] altogether by jumping straight from claim 1/[004] to Example 2. However, as discussed above, UPenn discloses different methods for synthesising modified RNAs – Example 2 provides one such method, but its use is not inevitable.

66. "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)" (**paragraph 51(b)**). This submission (including its reliance upon Figure 5) represents a significant expansion on PBNT's case at trial in relation to Example 7 and which the Judge addressed in §337. In any event it is misplaced for the following reasons.

67. It was CGK that various types of exogenous RNA were recognised by the innate immune system (§219). For most RNAs, reducing the immunogenicity of the molecule to the greatest extent possible is a desirable end in its own right. But in the case of mRNA, it is important to keep in mind that reducing immunogenicity is not the only consideration – the mRNA must also be translated efficiently. As the Judge found in §377, the skilled person would think that translation was of importance because the advance of UPenn over Karikó 2005 was in this area.

68. UPenn shows that the twin objectives of reduced immunogenicity and enhanced translation are consistently achieved with Ψ. However, that is not the case with the other nucleosides that were tested. Examples 10 and 11 (Figures 9 and 10) show that 100% replacement with m^5C impairs translation *in vitro* and has variable effects on translation in different cell types (either no improvement or increased translation). 100% replacement with m^5U dramatically reduces translation in one cell type and has no effect in the other. In the case of m^6A, 100% replacement completely abrogates translation *in vitro* and in both types of cell. Notably, Figure 10 also shows that the translation of mRNA containing m^6A can be improved (to the point that it is marginally better than unmodified mRNA) by

reducing the percentage of m^6A from 100% to 5%. See Rosenecker 1, ¶¶200-204 and Enright 1, ¶¶6.23-6.24 & ¶¶7.54-7.61. Thus, UPenn itself teaches that there is no inherent correlation between reduced immunogenicity and enhanced translation – it is not inevitable that 100% replacement will achieve both objectives.

69. As the Judge explained, the prior art is not a reservoir from which different features can be combined in the absence of a clear teaching to do so (§126). There is no clear teaching in UPenn to combine [004]/claim 1 with Example 7. Moreover, making that combination without regard to Examples 10 and 11 is precisely the kind of cherry-picking that the law deprecates.

70. "It was CGK that that immune suppression is proportional to the % of modifications" (**paragraph 51(c)**). Immune suppression was only known to be proportional to the number of modifications for *certain* modified nucleosides (§251(i)). It was never suggested (nor could it have been) that such proportionality extended to all modified nucleosides. As the Judge found, the skilled person would not know why Ψ had worked so well in UPenn (§382) and that even small structural changes can make a big difference in effect (§406). UPenn does not disclose, nor could the skilled person infer that any of the other nucleosides in [0056] would demonstrate the same proportionality.

71. Turning to PBNT's criticisms of the Judge, it is important to keep in mind the submissions that he was addressing in §337, as distinct from the arguments now deployed on appeal.

72. The Judge wrongly found that in Example 2 "a lesser percentage might be just as good" (**paragraph 52**). PBNT criticises the Judge's finding by reference to Example 7. This is not fair to the Judge – in the first three lines of §337, he was simply addressing PBNT's submission that Example 2 "*describes the in vitro synthesis of RNAs with 100% replacement*" (PNBT's Novelty chart, page 1). He rightly found that Example 2 does not make 100% replacement preferred.

73. "Necessity is not the correct standard for a pointer in this context" (**paragraph 53**). Again, this is not a fair criticism of the Judge. In the last sentence of §337, he was addressing PBNT's submission that "*Example 7 further teaches that the greater degree of modification, the greater the immunosuppression which is another reason to make 100% modified nucleosides*" (PNBT's Novelty chart, page 1). As the Judge rightly found, the whole purpose of Example 7 is to assess how much replacement would have what effect. There is no teaching in UPenn that the results in Example 7 will be achieved with nucleosides other than m^6A, m^5C and Ψ.

74. The Judge wrongly found that PBNT's pointers require "analysis" (**paragraph 54**). The Judge's reference to analysis was entirely appropriate given the absence of any express disclosure that 100% replacement is preferred.

75. The Judge wrongly relied on the absence of a direct link between PBNT's pointers and [0074] (**paragraph 54**). This amounts to little more than a complaint that the Judge rejected part of PBNT's case. PBNT sought to establish a preference for the 100% figure contained in [0074] by linking it to Examples 2 and 3. The Judge disagreed.

76. In summary, the Judge rightly concluded as he did in §338 – UPenn does not disclose that 100% replacement of the nucleosides in [0056] is preferred.

77. Even if 100% was disclosed as preferred, the Judge nevertheless rejected Route 3 for two further reasons (§339): first, the absence of any pointer to the *combination* of m1Ψ and 100% replacement; and second, the requirement to combine 100% replacement with something (m1Ψ) found in an unclear and apparently open-ended list ([0056]). We have already addressed the latter.

78. As for the absence of any pointer to the combination of m1Ψ and 100%, there is no dispute that the EPO's general approach is to look for a pointer to the *combination* of claim features (§139). However PBNT contends that "a selection from independent lists"-type analysis is not appropriate in this case as a matter of law and/or on the facts (**paragraphs 55 and 56**).

79. Starting with the law, the Judge considered the issue of independent lists in §145 with reference to a decision on which PBNT placed particular reliance, namely T1581/12. In that case, the Board held that the principle of not combining members of two fully independent lists in the absence of a clear pointer to the combination did not apply to the specific facts before it (¶7). The Judge derived little assistance from T1581/12, beyond the (unremarkable) proposition that in a case where there is no need to combine two lists, then the principle does not apply.

80. The additional decisions cited by PBNT in **paragraph 55** do not assist its case. In *Novartis v Dr Reddy's* [2019] EWHC 92 (Pat) at [29], Birss J (as he then was) articulated the same proposition as the Judge – every case has to be decided on its own facts. And T783/09 and T1259/16 are simply decisions in which different facts led to different outcomes. In T783/09, the application contained two lists (one with two members and the other with 22 members) representing 44 individual combinations, disclosed as "very preferred embodiments". For that reason, the Board held that claiming only three of the combinations did not add matter because it resulted from the deletion of 41 elements from

a list of 44 qualitatively equal elements (¶7). In T1259/16, the claim combined two features ("free of bromine" and "less than 100 ppm of metal ion impurities"), both of which were disclosed in the application but in separate lists. The Board held that the claimed combination added matter because the two lists were fully independent – the limits relating to free bromine and metal ion impurities could be varied independently (¶37).

81. So too in the present case – the modified nucleoside and percentage replacement can be varied independently. As the Judge held in §145, the identity of the modified nucleoside says nothing about the percentage incorporation. It is no answer that a scientist "*choosing to synthesise an mRNA containing m1Ψ in place of U necessarily has to choose a percentage of modified nucleoside to use*" (**paragraph 55**) because the scientist has two choices to make – which modified nucleoside to use and what percentage replacement. The former is unconnected with the latter and vice versa. For any particular modification other than Ψ, the appropriate percentage replacement cannot be derived from UPenn and would have to be determined empirically.

82. Moderna endorses the Judge's conclusion in relation to Route 3. As he explained in §146, pointers are a facet of deciding the question of clear and unambiguous disclosure and not a licence for holding something to be disclosed merely because it is alleged to be an obvious choice. The Judge evaluated UPenn in the light of the evidence and rightly concluded that it does not clearly and unambiguously disclose the combined features of claim 3: mRNA, m1Ψ and 100% replacement.

ROUTE 1

83. Example 31 [00290] refers to the introduction of additional nucleoside modifications into *in vitro*-transcribed RNA using the methods described in Examples 2 and 7 and testing their effects on immunogenicity and translation as described in Examples 1-8 and 9-15 respectively. It states that "*Certain additional modifications are found to decrease immunogenicity and enhance translation*" but those modifications are not identified.

84. [00291] contains a list of 96 nucleosides, comprising those named in [0070] and [0056], less Ψ. In other words, all the nucleosides in UPenn for which there are no experimental data. The list in [00291] is introduced as "*Modifications tested include e.g.*"

85. The question of 100% replacement does not arise in Route 1 because to the extent that the skilled person undertook Example 2 they would achieve complete replacement (§315). However, the cross-reference to Example 2 raises an issue concerning the types of RNA transcribed in that Example. There are five such RNAs specified in [00187]: RNA-1866,

RNA-1571, RNA-730, RNA-713 and RNA-497. One of them (RNA-713) is not an mRNA and another (RNA-497) was not tested. See §314 and §321(vi).

86. PBNT's case is correctly recorded in the Judgment at §314 and §318, that is to say m1Ψ is individually disclosed in [00291] and each of the RNAs in Example 2 is disclosed in combination with each of the 96 options from [00291]. As PBNT submitted in its Novelty chart (page 3):

> "*There is no requirement to select any of the features of either claims 3 or 5 from multiple lists, since carrying out Example 31 with Example 2 results in the skilled person making an mRNA falling within claims 3 and 5 of EP 949.*
>
> *As such, UPenn contains clear instructions to make something that would infringe those claims / clear and unmistakable directions to do what the patentee claims and is thus novelty-destroying*"

87. The Judge rightly rejected anticipation by Route 1 for the reasons given in §§321-327. We address PBNT's criticisms of the Judgment in the same order as they appear in its skeleton argument.

Alleged error #1

88. The first alleged error comprises a number of isolated attacks on the Judge's findings in §§321 and §§323-324 as to what Example 31 would be understood to disclose to the skilled person. To the extent that those findings are challenged, PBNT's criticisms are without foundation; they do not begin to establish any error of principle on the Judge's part.

89. "The unambiguous instructions are to go back and perform Examples 2 and 7 with additional modifications" (**paragraph 68**). PBNT criticises the Judge's characterisation of Example 31 as "*extremely tentative*" in §323. That was an entirely fair characterisation, not least in light of the Judge's earlier findings in §321(i)-(vii). PBNT also says that the Judge was wrong to find in §324 (first sentence) that Examples 2 and 7 provide methods that *may* be used because [00290] states that such methods *are* used. Again, PBNT overlooks the Judge's earlier findings, in particular at §321(ii) (which is not challenged). The Judge was plainly entitled to find as he did in the first sentence of §324, that finding being firmly rooted in the evidence before him.

90. Note that in the second sentence of §324, the Judge found that there is no teaching in Example 31 to "go back and redo Example 2 or Example 7 with the *exact RNA sequences disclosed there*" (emphasis added). That finding is not challenged.

91. "The reasons for testing additional modifications would be clear to the skilled reader" (**paragraph 69**). In §323, the Judge found that "*The extent of what [Example 31] is proposing and the reasons for doing it are both woolly*". PBNT's skeleton makes no mention of the former (the extent of what Example 31 is proposing). But it says that the reasons for testing additional nucleosides would be clear, namely to test their immunogenicity and translation efficiency. However this ignores the Judge's reference in §323 to [31] of *Dr Reddy's* in which Jacob LJ disparaged "*a mere woolly indication of the possible use of the compounds*". Thus, the Judge rightly found that the reasons are woolly because UPenn says nothing about the utility (nor likely properties) of any of the additional modifications. As Professor Rosenecker explained, the statement in [00290] that "*Certain additional modifications are found to decrease immunogenicity and enhance translation*" is uninformative, absent any identification of the nucleosides in question. (Rosenecker 1, ¶231)

92. The Judge was wrong to find that Example 31 is open ended (**paragraph 70**). In §321(iii), the Judge found that the whole tone of Example 31 is open-ended. He placed particular weight ("*the most concrete example*" as he put it) on the words "*include e.g.*" before the list of modifications in [00291], the consequence being that the list is of uncertain length (§327). The Judge was plainly right to find as he did. PBNT's construction (*the skilled person would not read "include e.g." as suggesting a wider pool*) ignores the plain meaning of "*include e.g.*" in circumstances where the CGK did not exclude the existence of a wider pool.

Alleged error #2

93. In §325, the Judge found that m1Ψ is not individualised in [00291]. PBNT challenges this finding on two grounds (**paragraphs 73-74**): first, by analogy with *Almirall*; and, second, by disputing the Judge's open-ended finding, which we have already addressed. As for *Almirall*, the submission appears to be that the Judge should have found that m1Ψ is individualised because 96 is less than 159 (the number of individualised compounds in *Almirall*). That submission is far too simplistic. Individualisation is not just a numbers game – context is also relevant (**paragraph 72**). The Judge was perfectly entitled to find that in the context of this case (specifically in the light of his earlier findings), the number of nucleosides identified in [00291] is too large.

94. In summary, the Judge rightly concluded that Example 31 does not clearly and unambiguously disclose, nor does it contain clear and unmistakable directions to make, each of the 96 nucleosides in [00291] in combination with each of the RNAs in Example 2.

Alleged error #3

95. As with Route 3, the Judge also rejected Route 1 on alternative grounds assuming (contrary to his earlier findings) that m1Ψ is individualised and Example 31 teaches the method of Example 2 using the exact RNA sequences disclosed therein. The Judge rightly concluded that even in these circumstances, anticipation required an impermissible selection from two lists (§§326-327). PBNT criticises the Judge's approach for two reasons.

96. If m1Ψ is individualised, there is no need for it to be preferred (**paragraph 75**). If m1Ψ is individualised, so too are all the other 95 nucleosides listed in [00291]. In the absence of any preference for m1Ψ, Example 31 cannot possibly constitute clear and unmistakable directions to test it, let alone in combination with one of the mRNAs in Example 2. As a last resort, PBNT suggests that the preference is provided by [0056] which we have addressed above. In any event, [0056] cannot help since it also discloses no preference for m1Ψ.

97. The synthesis of RNA-1866 with 100% m1Ψ is inevitable (**paragraph 76**). This submission is unsustainable in the light of the Judge's findings that the skilled person would not think they were being told to do all the possibilities in Example 31 (§321(iv)) and that there is no teaching to go back and redo Example 2 with the exact RNA sequences disclosed there (§324), neither of which is challenged.

ROUTE 2

98. Route 2 only comes into play in the event that the appeal under Route 1 would have succeeded but for the absence of any teaching to use the exact sequences disclosed in Example 2 or Example 7 (§318). Since that finding is not challenged, the submission in **paragraph 77** that there are sufficient pointers to select an mRNA from Example 2 is to no effect.

99. In any event, the submissions in **paragraph 78** do not advance matters. PBNT relies on the Judge's finding that "the skilled person would think that translation was of importance" (§377) but singularly fails to engage with the Judge's assessment of Route 2 in §§328-329. The Judge was right to reject Route 2 for the reasons that he gave.

OBVIOUSNESS: GROUNDS 1-3 (SKILLED PERSON) AND 7-9 (OBVIOUSNESS)

INTRODUCTION

100. The Judge's approach to obviousness, and his detailed reasoning, were entirely correct. The Judge's analyses of the skilled person and of obviousness were intertwined, and he explained how and why they interacted in §266, which we invite the Court consider at the outset.

101. In these circumstances, in order to get an appeal on obviousness off the ground, PBNT needs to identify a fundamental error of principle in the Judge's approach or findings. Nowhere is any such error articulated in PBNT's Grounds of Appeal or skeleton argument. Instead, each aspect of PBNT's appeal on obviousness goes to an alleged error of evaluation. In any event, PBNT's criticisms are wrong, as we discuss below.

102. There is no serious contention that the Judge misdirected himself as to the law. It would be surprising if there were. The law is clear and well-established, having been reaffirmed by the Supreme Court relatively recently in *ICOS*. Instead, PBNT's points are complaints about the Judge's impression of the witnesses, his findings in the light of their evidence, or the weight he gave to particular factors in the multi-factorial assessment of the statutory question.

103. On appeal, these complaints go nowhere. For example, in relation to expectation of success, the contention that the Judge erred in placing "*too much weight*" on this factor in his assessment (**paragraph 142**) is a non-starter.

104. Similarly, PBNT's points about the skilled team are simply an attempt to rehabilitate a witness who the Judge found to be less useful than Professor Rosenecker in helping him to understand how the skilled person would think and reason. There is no suggestion that the Judge misdirected himself about how to assess the appropriate skilled person. Indeed PBNT accepts that he was right to find at §266 that identifying the right skilled person was important to the assessment of obviousness in this case (**paragraph 88**).

105. The Judge's overall conclusion turned on the evidence. PBNT just does not like the way the Judge appraised and used that evidence when applying what it accepts is the correct test in law.

106. One aspect of the law bears emphasis, though, and it is a clear and consistent thread running through substantially all recent authority on obviousness. The assessment is not just multifactorial, but takes into account *all* the relevant facts and matters. It is in that

sense a *global* assessment – so that leaving relevant considerations out of account may in some circumstances be a ground for appellate reversal: *ICOS* at [81].

107. PBNT's appeal seeks to do precisely the opposite: it seeks to decontextualise and isolate certain factors in the analysis (expectation of success, motive) and then downgrade their importance by saying that on different facts they might not matter.

108. That is a *non sequitur*. Simply because a particular factor may not have much, or perhaps any, influence on one set of facts in no sense means it cannot be important – even decisive – on different facts.

109. For example, there may exist cases on different facts where the expectation of success is of lesser significance. But the present case is one in which the field had been starved of success for years and the prior art presents a package of excellent, reasoned and evidenced science showing that ψ is very promising – so promising that UPenn's authors stopped their work on everything else. The notion that a skilled person would not care about that and would just try some other chemistry at random, regardless of any prospects about whether it may or may not lead anywhere, is fanciful.

110. Decontextualising each element of this assessment in this way is apt to give a misleading picture. And that is why the law of obviousness – and the law about appeals from findings of (non-)obviousness – has the shape it does: the trial Judge is best placed to hear all the witnesses, to absorb the story they tell and the way they tell it, and thereby to have maximum context to make the full, global assessment.

111. The Judge heard all that evidence. And there was ample basis for his conclusion (the following references being examples only, accompanied by square-bracketed references to corresponding parts of the Judgment):

    (1) at least transcript therapy as "plagued with problems" by the priority date – Rosenecker XX, T3/pp448-449 and T3/p451/16-p452/5 – [§365];

    (2) the prior art gave a strong, clear message in favour of taking Ψ forward – in respect of UPenn, for example, see Enright XX T2/p282/11-22, and Rosenecker XX T4/p518/14-24 – [§§365-370];

    (3) what the skilled person would *not* glean from the prior art is any understanding of what it was about Ψ that made it promising – there was no teaching of any characteristic or chemical property that Ψ had that could be sought to be replicated

using some other modified nucleoside – e.g. (in respect of Karikó 2008), Enright XX, T2/p198/20-p199/2 – [§382];

(4) that lack of understanding imparts no direction to any decision-making about what modifications to test if, instead of taking forward the modification the prior art showcases (Ψ), the skilled person chose to investigate other modifications instead – Rosenecker XX T3/p441/4-8, p444/5-9, p453/16-24, p457/24-p458/8 and p461/23-p462/7 – [also §382];

(5) there was no motive for instead carrying out a directionless SAR-like project of the sort PBNT proposed, which Moderna characterised as a "scattergun approach", especially in light of (1) above – [§420];

(6) in particular, the modifications proposed by Dr Enright as allegedly-obvious next steps had no rational basis for choosing them – Rosenecker XX at T4/pp520-534, but see in particular p520/5-21, p521/13-24, p522/22-p523/20 and p530/23-p531/11, where Professor Rosenecker described the approach put to him, of just-test-it-and-something-might-just-work as *"a game. It is not real scientific work"* – [§382 again]; and

(7) there would be no reasonable expectation of success in relation to Dr Enright's proposed modifications – Rosenecker XX at T4/p494/17-23, p498/10-19 and p528/17-22 – [§§409-410].

112. That is in essence a complete answer to the obviousness appeal. The Judge's task was to hear and read the evidence, and to evaluate it. That he did. The evidence provides a solid basis for the Judge's evaluative conclusions. As part of that, at trial, the Judge heard from both experts, one of whom – Professor Rosenecker – was actually in the field at the time and so was able to give direct evidence, from his own experience, about the prejudices, frustrations and failures those people experienced. Those are an important part of the story on obviousness, to be weighed alongside the technical aspects of what the documents impart. In contrast, Dr Enright was not in any such field at the time, and so could not provide such direct insight.

113. A clear story emerged from the evidence. It hangs together, and it persuaded the Judge, imparted by an expert who was actually in the field. The Judge was entitled (to put it at its lowest) to be persuaded by it.

114. With that introduction, we address the issues in the same order as PBNT's skeleton argument.

The skilled person

115. Grounds 1 and 2 are alternative ways of expressing the same complaint – the Judge is said to have been wrong to reject PBNT's case that the skilled person includes an RNA biologist who is interested in using RNA for fundamental research (§256(ii)).

116. Moderna's position is very simple. The Judge followed the correct approach in law for identifying the skilled person and undertook a textbook analysis of the materials in the case. His findings of fact provide a complete answer to Grounds 1 and 2.

117. Regarding the law, the Judge adopted the guidance and structured approach in *Illumina v MGI* [2021] EWHC 57 (Pat) at [58]-[70]. This approach requires the Court to consider, amongst other things, the real situation at the priority date and what real research teams existed at the time (see §115(b), citing *Schlumberger Holdings v EMG* [2010] EWCA Civ 819 at [42])).

118. As for the facts, the Judge considered what real teams were doing at the priority date in §260. He found that there were real teams in a number of fields (cellular reprogramming studies, immunotherapy, direct vaccination etc.) where a solution to the problem that EP949 aims to solve could be useful. As PBNT says (**paragraph 95**), the list in §260 was based on what it had established in cross-examination by reference to a large volume of literature from a large number of real-life groups. The Judge found that PBNT's description of some of the fields as "study" or "research" (they were defined as such by PBNT in its closing submissions) was not a fair way of looking at things. He found that the teams "*were looking for practical results*" and that the correct field is not "*one of pure research, whatever its scope*." (§261)

119. At §263, the Judge concluded that the skilled person is "*someone with a knowledge of RNA biology, with a* ***practical*** *interest in improving the use of mRNA in relation to translation and immunogenicity in any of the fields above*." (emphasis added)

120. At §265, the Judge contrasted the skilled person with Dr Enright "*who is not from any of the subfields but rather a pure, basic scientist*". The Judge found that Dr Enright's interests were to do with fundamental research, well removed from the practical application of mRNA expression and much more at the theoretical end of the spectrum (§51).

121. Turning to PBNT's criticisms of the Judgment, it is not suggested that the Judge erred in law. Instead, the argument is that his rejection of PBNT's case is inconsistent with the list in §260 because that list includes a number of fundamental research fields, as exemplified by the use of mRNA encoded reporter proteins in sub-field (iv). (**paragraphs 98-105**)

122. There is no such inconsistency. Since PBNT has focussed on sub-field (iv), we shall do the same. In its closing submissions before the Judge, PBNT identified teams in this sub-field by reference to three publications: Giraldez 2006, Karikó 2008 and Rejman 2010. Taking them in turn:

(1) Giraldez 2006 is a classic piece of pure research. Dr Enright and others used an mRNA encoded reporter protein to validate zebrafish genes targeted in early embryogenesis by miR-430 (a microRNA – see §181). This work had nothing to do with seeking to increase the translation of mRNA. Nor did it have anything to do with reducing the immunogenicity of mRNA because the immunogenic effects of RNA are not a concern in zebrafish. See T1/p81/18-p85/19 and T1/p89/12-p90/9.

(2) In Karikó 2008, the authors used mRNA encoded reporter proteins to assess the effects of nucleoside modifications on the translation and immunogenicity of mRNA, the purpose being to improve the properties of IVT mRNA for use in the clinic (see Abstract and the Discussion).

(3) The same is true of Rejman 2010. This was a paper from de Smedt's group which was using mRNA for transcript therapy or were interested in doing so (Rosenecker 1, ¶26). In Rejman 2010, they used an mRNA encoded reporter protein in experiments designed to optimise the efficiency of transfection.

123. Thus Karikó 2008 and Rejman 2010 are publications from precisely the kinds of teams to whom the Judge was referring in §§260-261. The Judge was plainly *not* including Dr Enright's team, as can be seen from his rejection of "*pure research, whatever its scope*" in §261 and his reference to Dr Enright as "*not from any of the subfields but rather a pure, basic scientist*" in §265. The allegation of inconsistency is wholly misplaced.

124. Ground 3. The Judge was right to characterise Dr Enright as "*a pure, basic scientist*", not least on the basis of his findings at §51 and he was right to reject Dr Enright's approach to obviousness for the reasons given in §50(iv) and §266.

[0056] and hindsight

125. The Judge found that Dr Enright's approach was affected by hindsight in the light of three considerations: (1) Dr Enright's explanation for the inclusion of m^5D in [0056]; (2) his reliance on a paper cited in the RNAMD (Brand et al 1978); and (3) his heavy focus on [0056] relative to [00291]. (§§52-63)

126. Taking these in reverse order, we have addressed UPenn's teaching in relation to [0056] above. PBNT's skeleton makes no mention of Dr Enright's reliance on Brand.

127. As for m^5D, PBNT seeks to recast Dr Enright's evidence in ¶7.16 (as it did before the Judge) as no more than a statement of technical fact, namely that m^5D is most structurally similar to $m^1\Psi$ of the [0056] nucleosides – "*[t]hat is all Dr Enright was saying*" (**paragraph 115**). However, that is not all that Dr Enright was saying. He evidence was that the structural similarities between $m^1\Psi$ and m^5D would *explain* the latter's inclusion in [0056]. Of course, that explanation falls apart given that there are nucleosides in the RNAMD that are more structurally similar to other members of [0056] than m^5D is to $m^1\Psi$ but which do not appear in [0056]. The Judge considered Dr Enright's ¶7.16 in detail at §60. His reasoning was faultless.

128. The fact that Dr Enright was asked for his views on the CGK and the prior art before he was shown EP949 (**paragraph 111**) is irrelevant because Dr Enright knew about the importance of $m^1\Psi$ at the time he finalised his first report (§53). Nor is it relevant that Dr Enright would want to test all five of the [0056] modifications (**paragraph 117**) because his analysis was affected by knowledge of the importance of $m^1\Psi$ (§64).

Expectation of success

129. PBNT's submissions are predicated on the Judge being wrong as to the skilled person and/or hindsight on Dr Enright's part (**paragraphs 118-121)**. In any event, Moderna's primary answer to PBNT's complaint about expectation of success is very simple: the weight accorded to this one factor in a global assessment was a matter for the Judge.

130. Given the extensive way in which PBNT has set it out in writing, though, we engage with the points raised to show that not only are they not appellate points, they have no substance.

131. PBNT's first point (**paragraphs 122-124**) appears to be that the Judge was wrong to rely on the absence of any concrete expectation of success with regard to alternative modified nucleosides, because the skilled person would not understand why Ψ performed so well. The Judge was wrong, it is said, because such work on alternative modifications resulting in additional or similar benefits to those found for ψ would have been "useful".

132. That does not follow. Just because, once someone has decided to do some work and has carried it out, the product of that work is useful, in no sense means it was obvious to undertake the work. Still less does it mean that it is obvious to do that work instead of taking forward an option in respect of which the prior art confers great promise, particularly in a field starved of promise for so long. This is another prime example of how isolating and decontextualising particular elements of the global assessment is dangerous and apt to mislead.

133. At **paragraph 124**, PBNT's statement that the Judge found UPenn's Example 31 to be a *"positive teaching to look for other, better nucleosides"* is correct as far as it goes, but:

    (1) for all the reasons explored above, it is not a positive teaching in respect of any particular nucleoside(s); and

    (2) it is also notable that in UPenn, the authors did the opposite: once they saw and showed how well Ψ performed, they stopped testing anything else.

134. **Paragraphs 125-128** amount to a submission that because basic research could produce an output that was informative or interesting to the reader of the Patent, there is therefore a relevant "motivation" to do such basic research.

135. This is simply a further attempt to rehabilitate Dr Enright and the relevance of his views. Considered carefully, it serves to illustrate the problem with the central thread of PBNT's submissions: it reduces the notion of the skilled addressee to a nearly empty concept. A fundamental scientist is not motivated in the same way, and not subject to the same pressures and limitations, as an applied scientist who is trying to make something work for a purpose. Since s/he has a purpose in mind, the applied scientist has a meaningful notion of success: achievement of that purpose, or perhaps even an appreciable step towards it.

136. The fundamental scientist approaches things differently – with a completely open mind as to the outcome. S/he will be happy with whatever s/he finds out, because the only goal is to know more. So it was, as the Judge highlighted at §§406-407, that Dr Enright was interested even in modifications to RNA that would have a "catastrophic effect" in terms of their activity. That would be a clear step *away* from putting into effect the invention of the Patent, but Dr Enright would just be pleased to know more. No doubt that is an admirable trait in a fundamental scientist. But it bears no resemblance to the attitude of the skilled person in patent law.

137. As Lord Hodge explained in *ICOS* at [70], the need for a meaningful motive is part of the obviousness assessment (it was his seventh factor) that has basis in the case law of the TBA at the EPO. It has also long been a feature of the UK law. See example Goff LJ in *Hickman v Andrews / WORKMATE* [1983] RPC 147 at 169, Slade LJ in *Hallen v Brabantia* [1991] RPC 195 at 212 and Sir Donald Nicholls VC in *Mölnlycke v P&G* [1994] RPC 49 at 114.

138. PBNT's approach instead downgrades the notional skilled person from someone with a practical interest in putting the invention into effect to anyone who is curious about, or interested in, the patent.

139. Such an approach makes the definition of the skilled person almost trivial. A basic scientist could be the skilled person in every case, since if defined generally enough, a basic scientist can more-or-less always be interested in the fundament of a scientific document. But it does not make him/her the skilled addressee of that patent.

140. PBNT's submission has a further difficulty: it greatly expands the scope of what would be obvious to include anything that might be interesting or instructive after the fact simply because "upstream fundamental research underpins and feeds into downstream therapeutic research" (**paragraph 128**). On PBNT's approach it could be obvious to take almost anything forward, on the basis that all data are good data. Deeming a course of work to be "obvious", simply because after the fact it results in interesting or useful knowledge, would considerably broaden the concept of obviousness – with no basis in principle, policy or the law for doing so.

141. **Paragraphs 129-132** seek to unpick a finding of the Judge about technical matters on which he heard evidence. PBNT seeks again to isolate the issue from the context of the rest of the evidence.

142. The Judge's assessment of the significance of Charette & Gray was detailed, correct, and properly contextualised; he considered it at §§385-416. This was an issue the subject of complex scientific evidence, in large part oral, which the Judge weighed carefully.

143. PBNT's submission is untenable in light of appellate deference to such assessments of the factual/technical evidence. But it is also wrong. PBNT proceeds (**paragraph 132**) on the assumption that the theory set out in Charette & Gray would need to be tested and validated by the skilled person. But there is no basis for that; the skilled person is not motivated to do trials for the sake of it, or simply to know more, as the law cited above clearly emphasises. The Judge's conclusions on this point are spelled out clearly and comprehensively in §416 which we invite the Court to review.

144. The remaining points at **paragraphs 133-143** are expressly (and repeatedly) made as a submission that the Judge is said to have afforded too much weight to a factor in a multifactorial assessment. That is not a proper appeal point and we do not propose to address it any further.