

OPINION UNDER SECTION 74A

Patent	EP(UK) 1619249
Proprietor(s)	Academisch Ziekenhuis Leiden
Exclusive Licensee	
Requester	Mewburn Ellis LLP, on 9 March 2009
Observer(s)	
Date Opinion issued	4 June 2009

The request

- 1 The comptroller has been requested to issue an opinion as to whether claims 1-27 of EP (UK) 1619249 ("the patent") are inventive over the following documents:
 - D1 *J Clin Invest*; Vol 95, pp 515-520 (1995). Takeshima *et al.* "Modulation of in vitro splicing of the upstream intron by modifying an intra-exon sequence which is deleted from the dystrophin gene in dystrophin Kobe"
 - D2 *J Clin Invest*; Vol 100, pp 2204-2210 (1997). Shiga *et al.* "Disruption of the splicing enhancer sequence within exon 27 of the dystrophin gene by a nonsense mutation induced partial skipping of the exon and is responsible for Becker muscular dystrophy"
 - D3 *Mol Pharmacol*; Vol 58, pp 380-387 (2000). Karras *et al.* "Deletion of individual exons and induction of soluble murine interleukin-5 receptor-alpha chain expression through antisense oligonucleotide-mediated redirection of pre-mRNA splicing"
 - D4 *Genes & Dev*; Vol 7, pp 407-418 (1993). Watakabe *et al.* "The role of exon sequences in splice site selection"
 - D5 *Mol Cell Biol*; Vol 14, pp 1347-1354 (1994). Tanaka *et al.* "Polypurine sequences within a downstream exon function as a splicing enhancer".
 - D6 *Genes & Dev*; Vol 12, pp 1998-2012 (1998). Liu *et al.* "Identification of functional splicing enhancer motifs recognised by individual SR proteins".
 - D7 *J Biol Chem*; Vol 275, pp 29170-29177 (2000). Dirksen *et al.* "Mapping

the SF2/ASF binding sites in the bovine growth hormone exonic splicing enhancer”.

- D8 *Genomics*; Vol 2, pp 90-95 (1988). Monaco *et al.* “An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus”.
- D9 *J Med Genetics*; Vol 28, pp 304-311 (1991). Abbs *et al.* “A convenient multiplex PCR system for the detection of dystrophin gene deletions: a comparative analysis with cDNA hybridisation shows mistypings by both methods”.
- D10 *Mol Hum Repro*; Vol 11, pp 1098-1094 (1999). Hussey *et al.* “Analysis of five Duchenne muscular dystrophy exons and gender determination using conventional duplex polymerase chain reaction on single cells”
- D11 Sequence of Exon 46 of Dystrophin gene
- D12 Sequence of Exon 51 of Dystrophin gene

- 2 In particular, Mewburn Ellis (“the requester”) seeks an opinion as to whether the are inventive over the disclosure of documents D1 or D2, either alone or when combined with documents D3-D8. Documents D9-D12 are used by the requester to demonstrate what was known in the art regarding the deletions involved in muscular dystrophy at the priority date.

Observations

- 3 Observations in response to the request were received from the patent holder’s attorney, J.A. Kemp & Co (“the proprietor”) on 20 April 2009 (extended from 9 April 2009 with Comptroller’s discretion). These maintain that the invention involved an inventive step. The proprietor also challenged the admissibility of documents D1 and D2 as these documents are similar to two of the prior art documents considered by the EPO and found not to prejudice inventive step. The proprietor enclosed copies of these two prior art documents:

- D13 *Biochem Biophys Res Commun*; Vol 226, pp 445-449 (1996). Pramono *et al.* “Induction of exon skipping of the dystrophin transcript in lymphoblastoid cells by transfecting an antisense oligodeoxynucleotide complementary to an exon recognition sequence”.
- D14 *Brain & Dev*; Vol 18, pp 167-172 (1996). Matsuo. “Duchenne/ Becker muscular dystrophy: from molecular diagnosis to gene therapy”.

- 4 These documents originate from the same research group as D1 and D2, and the requester argues that D1 and D2 provide the same information to the person skilled in the art as D13 and D14 and do not add anything in substantive terms to the basis upon which the EPO granted the patent. In addition, the proprietor argues that D3-D7 are not relevant to the common general knowledge and therefore should not be

considered for inventive step purposes as they would not have been known to the skilled man working in the area provided by the patent.

- 5 The proprietor also provided a further document to demonstrate what was known in the art at the priority date of the patent:

D15 *Genes VII*, Lewin (2000), pp 704-705 “*Nuclear splicing*”. (Oxford University Press) ISBN 0-19-879276

Observations in reply

- 6 Observations in reply were received from the requester on 1 May 2009 that countered the challenges of the proprietor. The requester argues that D1 and D2 are admissible and should be considered for inventive step purposes. He also argues that documents D3-D7 should be considered for inventive step purposes as they are relevant to the problem that the patent intends to solve.

- 7 The requester also provided an additional document which was acknowledged in the patent as filed prior art:

D16 *Neuromuscular Disorders*; Vol 9, pp 330-338 (1999). Wilton *et al* “*Specific removal of the nonsense mutation from the mdx dystrophin mRNA using antisense oligonucleotides*”.

The patent

- 8 European patent application number 05076770.6 was filed on 21 September 2001, claiming priority from EP 00203283, which itself was filed on 21 September 2000. The patent was granted by the EPO on 24 September 2008, with the title “Induction of exon skipping in eukaryotic cells”.
- 9 The patent is intended to provide a therapy for Duchenne muscular dystrophy (DMD) by converting it to the less severe Becker muscular dystrophy (BMD). DMD is caused by the expression of a non-functional dystrophin gene, usually caused by a mutation or incorrect splicing that leads to the introduction of a stop codon or change in the reading frame of an exon. This leads to the premature termination of the expression of the dystrophin gene. BMD occurs where the mutation does not result in the premature termination of the dystrophin gene, and therefore a partially functional protein is produced. It is known in the art that deletion of an exon that do not result in alteration of the reading frame of the dystrophin protein produce a partially functional dystrophin that results in the BMD phenotype.
- 10 The patent provides a method of inducing exon skipping in the pre-mRNA for the dystrophin gene in order to generate a partially functional dystrophin gene. This method can be used to “skip” those exons where a stop codon is found, or an alteration in reading frame occurs, which would usually result in a truncated dystrophin and the DMD phenotype. By skipping these exons the reading frame of the protein is preserved and a partially functional dystrophin protein (deleted for the skipped exon) is produced, resulting in a milder BMD phenotype. The method uses antisense oligonucleotides directed at “exon inclusion signals” within the interior of

specific exons. It consists of 27 claims, including independent claims 1, 4, 8, 18, 19 and 25.

The claims

11 Independent claims 1, 4, 8, 18, 19 and 25 read as follows:

1. *Use of an antisense-oligonucleotide directed against the interior of exon 2, 8, 29, 43, 44, 45, 46, 50, 51, 52 or 53 in a dystrophin pre-mRNA, wherein said antisense-oligonucleotide is capable of specifically inhibiting an exon inclusion signal in said exon and contains between 14-40 nucleotides, for the preparation of a medicament for directing splicing of said dystrophin pre-mRNA in a cell capable of performing a splicing operation.*
4. *Use of an antisense-oligonucleotide directed against the interior of exon 2, 8, 29, 43, 44, 45, 46, 50, 51, 52 or 53 in a dystrophin pre-mRNA wherein said antisense-oligonucleotide is capable of specifically inhibiting an exon inclusion signal in said exon and contains between 14-40 nucleotides, for producing a mutant or normal dystrophin.*
8. *A method for directing splicing of a dystrophin pre-mRNA in a cell capable of performing a splicing operation comprising contacting said dystrophin pre-mRNA in said cell in vitro with an antisense-oligonucleotide capable of specifically inhibiting an exon inclusion signal of exon 2, 8, 29, 43, 44, 45, 46, 50, 51, 52 or 53 in said dystrophin pre-mRNA, said oligonucleotide containing between 14-40 nucleotides, said method further comprising allowing splicing of said pre-mRNA.*
18. *An antisense-oligonucleotide of between 14-40 nucleotides, comprising the nucleic acid sequence*

hAON#4: 5' CTGCTTCCTCCAACC
hAON #6: 5' GTTATCCTGCTTCCTCCAACC
hAON #8: 5' GCTTTTCTTTTAGTTGCTGC
hAON #9: 5' TTAGTTGCTGCTCTT
hAON #11: 5' TTGCTGCTCTTTTCC
hAON #21: 5' CCACAGGTTGTGTCACCAG
hAON #22: 5' TTTCTTAGTAACACAGGTT
hAON #23: 5' TGGCATTCTAGTTTGG,
hAON #24: 5' CCAGAGCAGGTACCTCCAACATC,
hAON #25: 5' GGTAAGTTCTGTCCAAGCCC,
hAON #26: 5' TCACCCTCTGTGATTTTAT,
hAON #27: 5' CCCTCTGTGATTTT,
hAON #28: 5' TCACCCACCATCACCT,
hAON #29: 5' TGATATCCTCAAGGTCACCC,
hAON #30: 5'CTGCTTGATGATCATCTCGTT

19. *A nucleic acid delivery vehicle comprising an antisense-oligonucleotide capable of inhibiting an exon-inclusion signal in at least one of exons 2, 8, 29, 43, 44, 45, 46, 50, 51, 52 or 53 of a dystrophin pre-mRNA said oligonucleotide*

containing between 14-40 nucleotides, or the complement of said oligonucleotide.

25. A non-human animal provided with an antisense-oligonucleotide capable of inhibiting an exon-inclusion signal in at least one of exons 2, 8, 29, 43, 44, 45, 46, 50, 51, 52 or 53 of a dystrophin pre-mRNA said oligonucleotide containing between 14-40 nucleotides.

12 In my assessment of the inventive step of the claims I will make a purposive construction of the claims, following the judgement of Lord Hoffman in *Kirin Amgen*¹. I will therefore interpret the claims in a way that I consider a person skilled in the art would have understood the patentee to mean by the language of the claim.

Scope of this Opinion

13 Before assessing inventive step of the claims I will compare the content of D1 and D2 provided by the requester with that of D13 and D14, considered by the EPO, as this will have a bearing on whether or not I issue an opinion in relation to D1 and/or D2.

14 The proprietor argues that D1 and D13 merely provide the same information to the skilled person, and that D1, D2, D13 and D14 have similar and related teaching. The requester, on the other hand, argues that D1 is more explicit in its teaching than D13, and that D2 provides further information about the splice sites and sequences than D13 and D14.

15 Rule 94(1)(b) states:

“The comptroller shall not issue an opinion if the question upon which the opinion is sought appears to him to have been sufficiently considered in any proceedings”

16 This reflects the intent of the opinion service to consider something new, and not go over old ground. Whilst the documents cited by the requester are *prima facie* different, do they add any new arguments over and above those considered before the EPO? It is clear from the examination proceedings that the inventive step objection raised by the EPO was based upon the knowledge that induced exon skipping using antisense oligonucleotides can be therapeutically applied to skip exons and that it can be applied to partially restore the function of the dystrophin gene. This is clearly demonstrated in those documents cited during the examination proceedings, with those documents including D13 and D14 cited herein. I have therefore considered if D1 and D2 cited by the requester add anything to this objection or if they simply form part of the original argument.

17 I have noted the proprietors arguments that D1 was produced from by same group as D13. In fact, D13 was produced a year after D1, and refers to D1 in its introduction. Both documents discuss the inhibition of splicing of intron 18 of the dystrophin pre-mRNA by the addition of an antisense oligonucleotide directed at a sequence internal to the purine-rich exon 19 of the pre-mRNA; the oligonucleotide

¹ *Kirin Amgen v Hoescht Marion Roussel Ltd* [2005] RPC 9

used in both documents is the same. Both documents demonstrate the same results and come to the same conclusion, that the exon-skipping method may have a use in therapy to restore some functionality to the dystrophin gene. Therefore, in terms of its technical contribution, D1, when considered in isolation, does not add anything to the argument over and above D13.

- 18 D2 also discusses the use of exon skipping to restore some functionality to the dystrophin gene, and also refers to D13 in its discussion. Whilst this document is also from the same group as D1 and D13, it relates to a different exon within the dystrophin gene, exon 27. However, this exon is another purine-rich exon, which is known to be necessary for the splicing of the upstream intron (see D13, page 445, third paragraph). Therefore, in my opinion, when considered in isolation this document also does not add any new arguments to those already considered before the EPO.
- 19 Consequently D1 and D2 do not add any further substantive information to the prior art over and above that provided by D13 and D14. Therefore, as they do not raise any new questions or arguments over those considered pre-grant by the EPO, in line with decisions BL O/370/07, BL O/298/07 and BL O/89/07 I will not provide an opinion on inventive step in respect of D1 and D2 when considered in isolation.
- 20 However, the requester has also provided further documents, D3-D7, which he suggests can be used in combination with D1 and D2 to provide new arguments. I agree with this assertion, as D3-D7 provide further insight into what was known about gene splicing at the priority date of the patent, and this knowledge can be considered in conjunction with the knowledge provided by D1 and D2. As this is a new argument to be considered, I am of the opinion that D1 and D2 are admissible when considered in conjunction with D3- D7, and will therefore consider the inventive step of the patent using this combination of documents.

Discussion

- 21 The requester considered the *Windsurfing*² test in their assessment of inventive step in the observations in reply; the proprietor did not directly consider this test in his arguments. I will use this test as recently reformulated in *Pozzoli*³. The assessment of inventive step using the *Windsurfing/ Pozzoli* approach is as follows:
- (1)(a) Identify the notional “person skilled in the art”
 - (1)(b) Identify the relevant common general knowledge of that person;
 - (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
 - (3) Identify what, if any, differences exist between the matter cited as forming part of the state of the art and the inventive concept of the claim or the claim as construed;

² *Windsurfing International v Tabur Marine (Great Britain) Ltd* [1985] RPC 59

³ *Pozzoli SPA v BDMA SA* [2007] EWCA Civ 588

- (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?
- 22 Neither the requester nor the proprietor considered the notion of the person skilled in the art; however both parties did address the issue of what is considered to be fall into the category of common general knowledge. In the observations, the proprietor referred to the decision of the Court of Appeal in *Wheatley vs Drillsafe Ltd*⁴ in that subject matter that does not constitute common general knowledge can only be combined with a disclosure of a specific citation under those circumstances where it would have been obvious to the person skilled in the art to combine the different disclosures. However, the requester countered this by arguing that the validity of the patent should be assessed not only in light of common general knowledge, but also in light of the prior art that the skilled person would identify as a starting point for tackling a new problem, and referred to the explanation of Warren J in *Actavis UK Ltd v Novartis AG*⁵.
- 23 Following the *Windsurfing/Pozzoli* test I will consider what constitutes the person skilled in the art before going on to consider what constitutes common general knowledge. In my opinion, the person skilled in the art would be one with a knowledge of the intron-exon structure of the dystrophin gene, and the variations in splicing that occur within this gene. Given that the problem to be addressed is the alteration of exon splicing of the dystrophin gene at the mRNA level, it is not unreasonable to assume that the person skilled in the art might seek advice from an expert in the general field of splicing, or might be a team of experts, one with the knowledge of the dystrophin gene, and one with the knowledge of exon splicing in general.
- 24 I am therefore in agreement with the requester in that there would be two fields of knowledge that could be combined to tackle the problem presented by the patent. The first relates to the dystrophin gene and its structure, and in particular the structure of the introns and exons and the effects of manipulation of this upon the functionality of the protein produced. In particular would be the understanding of its role in both DMD, where a non-functional, usually truncated, protein is expressed, and in the milder BMD, where a partially functional protein produced as a result of exon skipping. The second field of knowledge relates to the mechanisms of alternative splicing and exon skipping, and this knowledge can be applied to the dystrophin gene in an attempt to understand the mechanics of the alternative splicing and exon skipping that occurs in the different forms of muscular dystrophy.
- 25 It is also on this basis that I agree with the requester on the admissibility and relevance of documents D3-D7 to the common general knowledge.
- 26 The second step of the *Windsurfing/Pozzoli* test is to identify the inventive concept of the claims in question. There are six independent claims to be considered, but they are all based upon the same inventive concept. Both the requester and the proprietor agree that the general inventive concept is based upon the use of exon skipping to

⁴ *Wheatley vs Drillsafe Ltd* [2001] RPC 7

⁵ *Actavis UK Ltd v Novartis AG* [2009] EWHC 41 (Ch)

modify the function of the dystrophin protein and its subsequent effects upon the severity of DMD. The proprietor expands on this, and considers that the inventive concept lies in the type oligonucleotides that can be designed for treating DMD by inducing exon skipping at selected exons by binding to an exon inclusion signal in the interior of specific exons, resulting in the production of a partially functional dystrophin protein.

- 27 The requester argues that the requirement of the oligonucleotides as being capable of binding to the exon inclusion signal is “no more than a self-limiting functional requirement, as the exon inclusion signals are not clearly defined”. The proprietor suggests that this is an objection of clarity, and I am in agreement with this and therefore it is not a matter that I will consider as part of this opinion. As I am not providing an opinion on the clarity of the claims, I will accept the definition of this exon inclusion signal as provided in the patent, in that it is a sequence interior to the exon that is necessary for inclusion of the exon in the final mRNA transcript, and it may or may not comprise an exon recognition sequence. It should be noted that for the purposes of this opinion I consider that the terms exon recognition sequence (ERS) and exonic splicing enhancers (ESEs) all relate to sequences within the exons of the mRNA that are targets for at least one member of the splicing apparatus, and therefore are synonymous and interchangeable.
- 28 I therefore agree with the proprietor, in that the inventive concept of the claims is reliant upon the specific exons to be skipped, and the use of the antisense oligonucleotides to inhibit the exon inclusion signal and thereby inducing exon-skipping. Consequently, in my opinion, the inventive concept common to the independent claims is the use antisense oligonucleotides that are directed against the interior of exons 2, 8, 29, 43, 44, 45, 46, 50, 51, 52 or 53 in a dystrophin pre-mRNA to inhibit an exon inclusion signal in said exon and thereby directing splicing of the dystrophin pre-mRNA. In my assessment of the inventive step of the claims, I will first make a comparison of this common inventive concept with the prior art documents, before making an assessment of the inventive step of the individual claims.
- 29 The third step of the *Windsurfing/Pozzoli* test is to identify the differences between the documents cited as state of the art and the alleged invention. As the documents cited can be grouped into two separate areas of prior art, I will consider these groups separately.
- 30 The first group of documents, D1 and D2, disclose what is known about the splicing of the dystrophin gene and the role in the severity of muscular dystrophy. D2 demonstrates that exon 27 of the dystrophin gene, which includes a premature stop codon, and which should produce a non-functional truncated dystrophin protein resulting in the severe DMD, is skipped *in vivo*, thereby producing a deleted, partially functional dystrophin protein which results in the less severe BMD. This demonstrates that exon skipping can be an effective way to reduce the effects of a stop codon in the treatment of DMD. However, there is no suggestion of the use of an antisense oligonucleotide targeting sequences within an exon to skip that exon for therapeutic purposes.

- 31 D1 demonstrates an *in vitro* method of inducing exon skipping by the use of a 31 nucleotide antisense oligonucleotide complementary to a purine rich sequence within that exon to be skipped, and contemplates a use of this method in the treatment of DMD. The exon skipped in this system is exon 19 of the DMD gene, which is a known deletion in dystrophin “Kobe”. This document does suggest that this research could lead to a therapeutic application in the transformation of a DMD patient into a BMD patient, and that antisense oligonucleotides in general could be used in therapy. However, the document does not suggest any other exons to target for the proposed therapy, or any additional antisense oligonucleotides.
- 32 Neither D1 nor D2, which specifically relate to the splicing of dystrophin mRNA, disclose the modulation of splicing of the exons defined in the claims. I appreciate that the intron-exon structure of the dystrophin gene was known at the priority date of the patent, and this is demonstrated by Annex A and B of the request. Furthermore, it is evident from the prior art documents provided by the requester (D8-D10) that there are wide variations in which exons are deleted “in frame” in the dystrophin gene producing a shorter, lower molecular weight protein resulting in the BMD phenotype, and which deletions are present in the dystrophin gene resulting in a frameshifted mRNA encoding for a truncated abnormal protein resulting in the DMD phenotype. Indeed some of the exons known to be deleted are defined in claim 1.
- 33 It is therefore clear that the differences between the patent and the prior art of documents D1 and D2 is the choice of the exons claimed for use in the method of the patent, and also the targeting of the “exon inclusion signal” within the exon.
- 34 The second group of documents (D3-D7) demonstrate what is known in relation to splicing. They all demonstrate that sequences within the exon itself are of importance in splicing, specifically for the binding of elements of the splicing apparatus. None of these document refer to the dystrophin gene, and therefore the most obvious difference between these documents and the patent is that the methods they disclose have not been used for the dystrophin gene. However, the specifics of the methods used in these documents are also of importance and I will therefore consider these in relation to the patent.
- 35 Documents D3-D5 and D7 show that purine rich sequences within the exons are of importance for the splicing reaction, with D3 and D7 further demonstrating the modulation of splicing by targeting these purine rich sequences with antisense oligonucleotides directed at them; D7 targets both known and putative target sequences with oligonucleotides and observes the effects of these upon splicing. D3 also suggests the use of such a modulation in therapy. In summary, these documents demonstrate that the availability of purine-rich sequences internal to the exon are of importance for the splicing of that exon, and that targeting these sequences can interfere with the splicing apparatus and prevent splicing of the exon, resulting in exon skipping.
- 36 Document D6 presents a more general overview of the ESEs recognised by the splicing factors, and provides a motif-search algorithm to search for a consensus sequences amongst identified ESEs. This document does suggest that a diverse set of sequences can act as ESEs, and that these are not necessarily purine rich sequences; however there is some degree of degeneracy in these sequences.

- 37 The requester considers that the methods of D3-D7 can be grouped into two: an empirical approach as in D3, and a more systemic approach as in D4-D7. I agree with this and therefore will consider these documents as members of these two groups. I have noted the arguments of the requester that D3 does not seek to identify those sequences involved in exon skipping by targeting the antisense oligonucleotides against specific sequences. Instead, the authors generate a series of oligonucleotides with overlapping sequences spanning the entire exon. They then test these antisense oligonucleotides for their ability to induce exon skipping. The requester argues that this approach could be used to identify an ESE within exons, and could be used to identify these sequences within known dystrophin exons, thereby arriving at the exons claimed.
- 38 I have considered the arguments of the proprietor, in that D3 is primarily concerned with the targeting of the 3' splice site. Whilst I appreciate that, as noted in the observations in reply, amongst the most active oligonucleotides are two that are directed interior to the exon, in my opinion the "take home message" in D3 is that targeting the 3' splice site is an effective way of targeting exon deletion. In light of this, in my opinion, a skilled person reading D3 and wishing to induce exon skipping in any gene, would be minded to test antisense oligonucleotides directed at the 3' splice site and not at the interior of the exon. Therefore, even if a skilled person intended to use such an approach to scan all exons in a specific gene, the teaching of D3 would direct a skilled person away from testing antisense oligonucleotides directed towards the interior of the exons. The patent claims the use of sequences internal to the exon and therefore this is a clear difference between the method used in the invention and the teaching of D3.
- 39 The "systemic" approach provided by D4-D7, according to the requester, provides a more focussed approach to looking for exonic splicing enhancers, using oligonucleotides directed at these potential sites, and I agree with this analysis. These documents in particular discuss the role of purine rich sequences in the ESEs, and would direct a person skilled in the art towards searching for such purine rich sequences in an exon in order to locate the ESEs. These ESE's are internal to the exon, as is the exon inclusion signal of the patent. However, the ESE's contain a purine rich sequence, which is not necessarily the case with the exon inclusion signals of the patent.
- 40 Therefore, to summarise, the patent differs from D1-D7 in the use of antisense molecules to target exon inclusion signals, which may or may not be purine rich, in exons 2, 8, 9, 29, 43, 44, 45, 46, 50, 51, 52 or 53 and induce exon skipping of the dystrophin gene.
- 41 The next step is to consider whether the differences constitute steps that would have been obvious to the person skilled in the art, or whether they required any degree of invention. In other words, would it have been obvious to a person skilled in the art to combine the teachings of D1 and D2 with that of D3-D7 in order to use antisense molecules to target exon inclusion signals in exons 2, 8, 9, 29, 43, 44, 45, 46, 50, 51, 52 or 53 and induce exon skipping of the dystrophin gene .

- 42 The proprietor has not provided any substantive arguments regarding the relevance of documents D3-D7 to the inventive step of the present application when combined with the teachings of D1 and D2; the proprietor merely deems D3-D7 irrelevant for not suggesting the use of an oligonucleotide directed and an exon inclusion signal for treating DMD. I do agree with the proprietor in that these documents do not suggest the use of antisense oligonucleotides for the treatment of DMD, but I am not considering these documents in isolation, rather I am considering them in combination with D1 and D2.
- 43 I agree with the requester in that a skilled person wishing to manipulate splicing of the dystrophin gene, and being aware of the teachings of D4- D7 might be directed towards searching for the purine rich sequences within the exons as potential targets for antisense oligonucleotides. However, it is clear from D6 that the process is not as straightforward as simply identifying purine rich sequences. I refer in particular to the final paragraph of the discussion, on page 2009, where the authors state that “...it is likely that many natural sequences that match the simple motifs identified in this study will fail to function as ESEs unless they are placed in an appropriate context”. The authors demonstrate that not all putative ESEs do in fact signal for the inclusion of the exon in the final transcript, and therefore in light of this I consider that it cannot be assumed that all putative ESEs would in fact be suitable targets for an antisense oligonucleotide.
- 44 Therefore, would a skilled person looking to manipulate the splicing of the dystrophin gene, and taking into account what is known about ESEs from D4-D7, be directed towards the exon inclusion signals interior to the exon? There is no doubt that they would look for putative ESEs interior to an exon, but as stated in D6 this is not necessarily sufficient for the exon to be included in the splice transcript. However, the putative ESEs would be a starting point as a target for an antisense oligonucleotide, and therefore a specific exon inclusion signal could be identifiable from amongst these ESEs.
- 45 Nevertheless, there remains the question of the targeting of exons 2, 8, 9, 29, 43, 44, 45, 46, 50, 51, 52 or 53. The proprietor has not provided any arguments as to the inventiveness of the specific exons claimed. In the observations in reply, the requester has applied the four step *Windsurfing* test to the inventive step of the choice of exons to be targeted. However, the requester has also divided the exons claimed into two groups, one in respect of exons 29, 46 and 51, for which data is provided in the patent, and one in respect of exons 2, 8, 43, 44, 45, 50, 52 and 53, for which no target sequences are disclosed in the specification.
- 46 In the observations the proprietor has acknowledged that the skilled person could search for purine rich sequences in the exons of the dystrophin genes in order to identify ESEs, but refers to D1 and D2 which state that only a few of the dystrophin gene exons comprise such purine rich sequences. In the observations in reply, the requester has argued that claimed exons 46 and 51 do in fact comprise purine rich sequences, which presumably is intended to show that this could make these exons at least targets for the identification of ESEs. However, the inventive concept is not merely the identification of an ESE, it is the identification of a sequence within the dystrophin pre-mRNA which specifically signals for the inclusion of that exon in the spliced mRNA transcript, and the broad approach of searching for a purine-rich

region may not result in such a sequence; therefore merely identifying the exons based upon their purine content may not be sufficient (as highlighted in D6).

- 47 The inventive concept is also concerned with the use of antisense oligonucleotides directed to these sequences, and the assertion that these oligonucleotides can lead to exon skipping within the dystrophin gene. D1 discloses the use of such a method for exon 19 of the dystrophin gene. In the observations, the proprietor has argued that this document is limited in its disclosure to exon 19, and that the system used in D1 is an artificial cell-free system that is not representative of what might occur in myocytes *in vivo*. This argument is substantiated, according to the proprietor, by the teaching of D15, which provides more insight into the parameters that can have an effect upon splicing. The requester countered this by stating that the authors of D1 anticipated their observations as being useful to induce exon skipping of other dystrophin exons, and in the development of therapeutics for DMD.
- 48 Whilst I agree that this document does suggest that exon skipping might be useful in the development of therapeutics for DMD, there is nothing in this document or any other document cited as prior art or otherwise, that would direct a skilled person towards the use of antisense oligonucleotides towards those specific exons defined in the claims. Therefore, even though means for identifying ESEs are known in the art (as demonstrated by D3-D7), and the use of oligonucleotides for inducing exon skipping in dystrophin pre-mRNA (as shown in D1), it is my opinion that there is nothing in the art that would direct a skilled person towards the use of antisense oligonucleotides directed at an exon inclusion signal interior to the exon to induce exon skipping of exons 2, 8, 9, 29, 43, 44, 45, 46, 50, 51, 52 or 53 of the dystrophin gene.
- 49 I have noted the reference of the requester to decision T 1329/04⁶ of the Technical Board of Appeal at the EPO, in that the invention should solve a technical problem and not put forward one, and therefore by merely asserting the use of exon 2, 8, 43, 44, 45, 50, 52 and 53, without any experimental data, the patent is merely putting forward a new problem. However, this decision is based upon the “problem/ solution” approach used by the EPO to assess inventive step. This approach lacks the same weight in UK law as the *Windsurfing/ Pozzoli* test. Nevertheless, a solution has been put forward, the skipping of specific exons to alter the dystrophin protein produced, and even if I were to use the problem/ solution approach I would come to the same conclusion.
- 50 Consequently, on balance, it is my opinion that it would not have been obvious to combine the teachings of D1 and D2 with the teachings of D3-D7 in order to induce exon skipping in exons 2, 8, 9, 29, 43, 44, 45, 46, 50, 51, 52 or 53 of the dystrophin gene. Moreover, it would not have been obvious to target the exon inclusion signal interior to the exon, and therefore the differences between the patent and the prior art would not have been obvious to a person skilled in the art and therefore do require some degree of invention.
- 51 I will now consider the inventive step of each independent claim in turn. Claim 1 defines the use of the antisense oligonucleotides of the invention in the preparation

⁶ T 1329/04 *Johns Hopkins/ Factor-9* (not reporter)

of a medicament for directing the splicing of dystrophin pre-mRNA. Whilst D1 and D2 suggest the use of antisense oligonucleotides in therapy, there is nothing to suggest the therapeutic benefit of using antisense oligonucleotides as provided by the patent. I have noted the requester's comments that there is no data supporting therapy in a patient; however, this is a support issue that does not form part of this opinion. Consequently, I consider that claim 1 is inventive over D1-D7.

- 52 Claim 4 defines the use of the antisense oligonucleotides of the invention for producing a mutant or normal dystrophin. Whilst it is clear from D1 that antisense oligonucleotides can be used to alter the splicing of the pre-mRNA transcript, again there is nothing to suggest the use of such oligonucleotides to induce exon skipping as provided by the patent. I have also noted the requester's comment that the invention does not provide what is claimed in the context of a normal dystrophin; again this is a support issue which does not form the basis of this patent. I am therefore of the opinion that claim 4 is also inventive over D1-D7.
- 53 Claim 8 relates to a method of directing splicing of a dystrophin pre-mRNA in a cell using the antisense oligonucleotide as defined above, and allowing splicing of the pre-mRNA. The requester argues that the method is merely an obvious alternative to the same technique applied to other exons of the same gene in the prior art (ie as disclosed in D1), but for the reasons I have given above it is my opinion that it would not be obvious for a skilled person to target the exon inclusion signal within those specific exons defined in the claim. Therefore I consider that claim 8 is also inventive over D1-D7.
- 54 Specific antisense oligonucleotides are defined in claim 18, and although the requester considers that these are the result of the obvious application of the prior art, in my opinion there is nothing in the prior art that would lead the skilled person to oligonucleotides comprising these specific sequences. Claim 18 is therefore also inventive over the prior art.
- 55 Claim 19 defines a nucleic acid delivery vehicle comprising an antisense oligonucleotide of the invention. The requester argues that this claim is merely an incorporation of the oligonucleotides of claim 18 into known delivery vehicles. However, as I consider that the antisense oligonucleotides of claim 18, and indeed any antisense oligonucleotide directed at the interior of the specific exons as defined in the claims are inventive over the prior art, I am also of the opinion that claim 19 is inventive.
- 56 Claim 25 provides a non-human animal comprising the antisense oligonucleotides of the invention. I have considered the requester's argument that in order to develop the medical use of claim 1 to the point where it could be tested on a human subject, suitable animal testing would be carried out. However, I have already considered that claim 1 is inventive, and therefore following the logic of the requester, claim 25 will also be inventive. Notwithstanding this argument, as I am of the opinion that the antisense oligonucleotides of the invention are inventive, I am also of the opinion that claim 25 provides an inventive step.

57 Therefore, in my opinion, claims 1, 4, 8, 18, 19 and 25 are inventive over the disclosure of either one of D1 or D2 when combined with any one of D3-D7. Consequently, appendent claims 2, 3, 5-7, 9-17, 20-24, 26 and 27 are also inventive in light of this document.

Opinion

58 I conclude that all of the claims involve an inventive step in light of D1-D7 submitted by the requester.

R. Dinham
Examiner