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***JH Corporate Services Pty Ltd v Sigma-Aldrich Co. LLC* [2021] APO 22**

Patent Application:	2018229489
Title:	CRISPR-based genome modification and regulation
Patent Applicant:	Sigma-Aldrich Co. LLC
Opponent:	JH Corporate Services Pty Ltd
Delegate:	Damian Triffett
Decision Date:	2 June 2021 (corrected on 4 June 2021)
Hearing Date:	10 November 2020, in Canberra via video conference
Catchwords:	**PATENTS** – section 59 opposition to grant of a patent – proposed amendment to the statement of grounds and particulars allowed – lack of clarity not established – lack of clear enough and complete enough disclosure not established – right to earliest priority date established – lack of novelty and inventive step not established – lack of support not established – lack of best method of performance not established – lack of utility not established – lack of manner of manufacture not established
Representation:	Counsel for the applicant: Benjamin Fitzpatrick Patent attorney for the applicant: Andrew Lee of Pizzeys Patent and Trade Mark Attorneys Counsel for the opponent: Katrina Howard SC and Ben Mee Patent attorney for the opponent: Dr Grant Shoebridge of Pearce IP

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Patent Application:	2018229489
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Date of Decision:	2 June 2021 (corrected on 4 June 2021)

DECISION

The opposition fails on all grounds. Subject to appeal, I direct that the application proceed to grant.

I award costs according to Schedule 8 against JH Corporate Services Pty Ltd.

REASONS FOR DECISION

Background

1. Patent application 2018229489 in the name of Sigma-Aldrich Co. LLC (**the applicant**) was advertised as accepted on 6 December 2018. JH Corporate Services Pty Ltd (**the opponent**) opposed the grant of a patent under section 59 of the *Patents Act 1990* (Cth) (**the *Patents Act***).

The opposition

2. The Statement of Grounds and Particulars (SGP) identified eight grounds of opposition: manner of manufacture, novelty, inventive step, utility, clear and complete enough disclosure, support, best method of performance and clarity. At the hearing, all eight grounds were pressed.

3. The opponent submitted a SGP on 6 June 2019. The opponent submitted an amended SGP on 16 September 2019 which was allowed on 3 October 2019. The opponent submitted a further amended SGP on 31 August 2020, and a Delegate of the Commissioner requested further information on 22 September 2020 and 20 October 2020. The opponent provided further information regarding the proposed amendments to the SGP on 27 October 2020 and requested to be heard in the event that the Commissioner is not disposed to allow the amendments on the basis of these submissions. On 3 November 2020, a Delegate wrote to the parties informing them that the matter will be referred to the Delegate to determine

allowability of the SGP amendment as part of the hearing deciding the substantive opposition.

4. The parties relied upon evidence by several declarants. Evidence in Support (EIS) consists of a declaration by Peter D. Currie (Currie-1). Evidence in Answer (EIA) consists of a declaration by Paula Cannon (Cannon). Evidence in Reply (EIR) consists of a declaration by Peter D. Currie (Currie-2). While a declaration was also provided by Peter Whitehead (Whitehead) in the EIR, for the reasons provided later in this decision, this declaration was not allowed and does not form part of the evidence for this opposition.

5. The request for examination in relation to the patent application was filed on 28 October 2018. Consequently, the amendments of the *Patents Act* brought about by *the Intellectual Property Laws Amendment (Raising the Bar) Act* 2012 (Cth) (**the *Raising the Bar Act***) apply to the present application. This includes section 60(3A) of the *Patents Act*, which provides that the Commissioner may refuse an application if satisfied on the balance of probabilities that a ground of opposition exists. It is the opponent who carries the onus of proof.

Allowability of the amendments to the SGP

Relevant Law

6. Regulation 5.16 of the *Patents Regulations 1991* (Cth)(**the *Patents Regulations***) provides:

"**5.16 Statement of grounds and particulars**

(1) An opponent may request the Commissioner in writing to amend the opponent's statement of grounds and particulars:

(a) to correct an error or omission in the grounds of opposition; or
(b) to update the grounds of opposition to reflect an amendment to the patent request or complete specification to which the statement relates; or
(c) to amend the facts and circumstances forming the basis for the grounds.

(2) The Commissioner must:

(a) notify the applicant of the opponent's request; and
(b) give the parties an opportunity to make representations about the amendment.

(3) The Commissioner must not make the amendment if:

(a) the Commissioner is considering an application for dismissal of the opposition under Part 5.4; or

(b) for an opposition begun under subregulation 5.4(1):
(i) the applicant's complete specification is being re-examined; and
(ii) the re-examination is not completed as required by regulation 9.5.

(4) The Commissioner must make the amendment if:

(a) subregulation (3) does not apply; and
(b) the Commissioner is satisfied that the amendment should be made.

(5) The Commissioner must, as soon as practicable:

(a) notify the parties of the Commissioner's decision; and
(b) if the Commissioner decides to make the amendment--give the applicant a copy of the amended statement”

7. Relevant factors to be taken into account in determining whether it is appropriate to make the amendment include:

- the prospect of undue prejudice to a party – for example, the applicant may be unduly prejudiced by unnecessary delays in seeking amendment, or by the introduction of further particulars that change the case the applicant has to answer (see *Diamond Scientific Company v CSL Limited* [1992] APO 55)(**the *CSL decision***);
- the timing of the amendment request and the reasonableness of the explanation of the delay;
- the public interest – noting that a correct determination of the opposition is one based on the issues properly raised in the opposition proceedings.[1]

Proposed amendment to the SGP

8. The opponent submitted a further amended SGP on 31 August 2020. The amended SGP did not add any further grounds of opposition. The amended SGP made three changes that were under dispute. The first was an added paragraph outlining that the experimental results do not demonstrate insertion of a donor sequence into a target chromosomal sequence. The second related to some paragraphs added under the ground of manner of manufacture. The third was the addition of some further statements relating to what was considered common general knowledge.

9. At the hearing, I asked the parties whether they would like a further opportunity after the hearing to provide evidence on the allowability of the SGP and both parties said they were satisfied with how they presented their case. I will now look at each of the proposed changes to the SGP in turn.

<u>Experimental results regarding the insertion of a donor sequence</u>

10. The amended SGP adds the following paragraph on page 3 under the heading “Priority date of the claims”:

> “The claims of the Opposed application encompass methods for insertion of a donor sequence into a target chromosomal sequence. However, the experimental results described in the priority documents demonstrate that targeted integration of a donor sequence did not occur using the CRISPR-Cas9 methods covered by the claims.

[1] *CSL Limited v Isonova AB et al.* [2016] APO 82.

Therefore, the disclosure of the priority documents does not enable the scope of the claims of the opposed application."

and adds a similar paragraph on page 7 under the ground of utility:

"The claims of the Opposed Application encompass methods for insertion of a donor sequence into a target chromosomal sequence. However, experimental results shown in Figure 5 of the Opposed Application demonstrate that targeted integration of a donor sequence did not occur using the CRISPR-Cas9 methods covered by the claims."

11. The applicant submits that this new assertion that the experimental results disclosed in the priority documents demonstrated that the integration of the donor sequence "did not occur" is a significant new particular, and quite different to the evidence in support of Professor Currie, and that, if this particular had been included in the original pleading, it is reasonable to assume the applicant would have dealt more directly with this assertion in its EIA.[2] In response, the opponent submits that all of the amendments are consistent with, and fully supported by, the opponent's evidence,[3] which the applicant answered.[4]

12. Turning now to the EIS, the evidence of Professor Currie makes the following statements in relation to the experimental results not demonstrating targeted integration of a donor sequence:

"When asked if I could draw a conclusion based on the results of Example 4 alone as to whether any of experiments A-D resulted in *integration of the GFP into the target locus* [emphasis added], I was very sceptical."[5]

"Therefore, I cannot conclude that there has been any successful integration of the GFP on this basis [Figure 4] alone."[6]

"When the GFP has been successfully integrated into the target genome locus of the cell, the forward and reverse primers should, according to Example 5, amplify a 1388 base pair fragment of DNA."

"Based on Figures 1 and 2, I conclude that each of experiments B, C and D failed to result in integration of GFP in the target DNA sequence in the cell."[7]

13. In response to the evidence of Professor Currie, the applicant's expert, Professor Cannon, provides detailed comments on the relevant examples in the earliest priority document for the opposed application (P1), noting that the relevant examples and results in P1 are the same as those in the opposed application.[8] In particular, Professor Cannon states at [62] that:

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[2] Applicant's Correspondence dated 6 October 2020.
[3] Currie-1 at [117]-[126]; Currie-2 at [19]-[22].
[4] Opponent's Correspondence dated 27 October 2020.
[5] Currie-1 at [122].
[6] Currie-1 at [122].
[7] Currie-1 at [124].
[8] Opponent's Correspondence dated 27 October 2020; Cannon at [25]-[64].

"Even one correctly sized PCR product in reactions A-D in Figure 2 of Chen P1 provided evidence to the skilled person which supported the conclusion that Example 4's very clear FACS results were indeed detecting site-specific integration of the GFP-encoding donor sequence" and that "[t]his would be taken as confirmation that … insertion of the exogenous DNA into the target sequence had occurred."

14. The SGP as originally filed states:

> "Lack of entitlement to the priority dates of documents P1, P2, P3 and P4 includes but is not limited to, for example, the following features referred to in the independent claims of the Opposed Application.
>
> …
> "integrating donor sequence", without limitation on the sequence."

15. Under regulation 5.16(c), the opponent may request to amend their SGP to amend the facts and circumstances forming the basis for the grounds. I have reviewed the original SGP, the SGP as opposed to be amended and the submissions of both parties and consider that this added particular is of little prejudice to the applicant.

16. While this particular was indeed new, there is nothing in the *Patents Act* or the case law that explicitly prohibits adding a new particular. The SGP as originally filed did question the priority date of the claims in relation to the "integrating donor sequence", and raised the grounds of utility, clear enough and complete enough disclosure and support. One factor to consider in the *CSL decision* is the public interest, noting that a correct determination of the opposition is one based on the issues properly raised in the opposition proceedings. I consider the issue regarding the integration of the donor sequence is central to a "correct determination" of the opposition, and further consider that the issue has been "properly raised" as the issue was raised in the opponent's EIS, and was addressed in the applicant's EIA, as exemplified by the passages from the evidence outlined above. While there may be *some* prejudice to the applicant, and potentially the applicant may have dealt with this issue more directly in its EIA, I consider that this issue was sufficiently dealt with in the applicant's EIA.

<u>Particulars under manner of manufacture</u>

17. The SGP as proposed to be amended added the following paragraphs on pages 4 and 5:

> "It is apparent on the face of the specification that the invention does not satisfy the threshold test for patentability as laid down in *NV Philips Gloeilampenfabrieken v Mirabella International Pty Ltd* (1995) 183 CLR 655.
>
> 1.1.1 The invention as claimed in the Opposed Application was described in Jinek (2012), which is referred to in paragraph [00236] at page 101, reference 7, of the Opposed Application, which is incorporated by reference at paragraph [0003]: see *Merck & Co Inc v Arrow* (2006) FCAFC 91"
>
> …

> "Further or in the alternative, the claims merely represent the use of a combination of known components, the known properties of which make them suitable for that use: see *Commissioner of Patents v Microcell Ltd* (1959) 102 CLR 232."

18. The applicant submits that the opponent introduced another substantive new particular that the claimed invention is not a manner of manufacture based on the Jinek (2012) publication (**the Jinek paper**).[9] The opponent responded by submitting that the evidence upon which the new particular was based, was set out in the opponent's EIS,[10] where Professor Currie discussed the Jinek paper which is central to the opponent's obviousness case.[11] The opponent further submits that Professor Cannon has already commented on the Jinek paper in EIA.[12]

19. With regard to the addition of the threshold test in *NV Philips Gloeilampenfabrieken v Mirabella International Pty Ltd*, and the addition of the statement of the law in *Commissioner of Patents v Microcell Ltd*, I note that while these case names were not present in the SGP as originally filed, the statements of the law that they represent were.[13] As a result, I consider adding these cases into the SGP is not adding a new particular but merely further characterising an old particular and is of no prejudice to the applicant. Furthermore, with regard to the Jinek paper, as the SGP as originally filed included a statement that the alleged invention did not meet the threshold of ingenuity required to be considered an invention, and the fact that Professor Currie discussed this paper as part of the opponent's obviousness case, and Professor Cannon had already commented on it, I consider that further characterising this particular to highlight the reference to the Jinek paper in the opposed application, is also of no prejudice to the applicant.

<u>Further statements on common general knowledge</u>

20. The SGP has also been proposed to be amended to include further statements of what was considered common general knowledge at the earliest priority date. To my mind, the most contentious of these inclusions are statements regarding targeted introduction of donor nucleic acid into a nucleic acid in a eukaryotic chromosome using ZFN and TALE nucleases, gene editing methodologies including the Cre-LoxP system and bacteriophage-derived integrases such as phiC31, as well as methodologies for regulating expression of genes including the Lac operator/repressor system.

21. The applicant argues that these proposed amendments to the SGP seek to introduce substantive new features of common general knowledge, and there is no explanation how these additional particulars will be deployed by the opponent in its case. The opponent submits that these new statements of common general knowledge either correspond to Professor Currie's EIS,[14] or were responding directly to the evidence put forward by Professor Cannon in relation to the range of unknowns left unanswered by the Jinek paper.[15] In particular, Currie-1 discusses TALEN and ZFN methodologies and their use in

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[9] Applicant's Correspondence dated 6 October 2020.
[10] Opponent's Correspondence dated 27 October 2020.
[11] Currie-1 at [49]-[64].
[12] Cannon at [66]-[106].
[13] See Particulars 1.1, 1.3 and 1.4 on page 3 of the SGP as originally filed.
[14] Currie-1 at [35]-[40].
[15] Opponent's Correspondence dated 27 October 2020; Currie-2 at [34]-[41] and [67].

the art,[16] and Currie-2 discusses the state of the art surrounding the Cre-LoxP system, protein integrases such as phiC31 and the Lac operator/repressor system.[17]

22. I agree with the opponent's submission and consider that these statements of common general knowledge are only of minimal prejudice to the applicant. The statements provided by Professor Currie in the EIS were done so under the heading of "Common general knowledge at 6 December 2012", and as common general knowledge is dealt with under the ground of inventive step, I think the applicant had fair notice of the case they had to answer. Furthermore, the statements of common general knowledge discussed in the EIR are considered directly in response to the EIA, therefore are of minimal prejudice.

Consideration

23. The opponent submits that unlike the *CSL decision*, which considered the addition of lack of best method and novelty in view of a document initially cited for inventive step, the amendments in the present case relate to the evidence that was obtained from the expert, Professor Currie.[18] The opponent further submits that the amendments to the SGP would not hamper the preparation of the applicant's case because they make the SGP consistent with the evidence, and it is in the public interest that the SGP and the evidence are consistent.[19] The opponent further argues that the case the applicant has to answer is the same as set out in the evidence as filed and therefore the amended SGP gives rise to no undue prejudice to the applicant.[20] The opponent concludes therefore, that the timing of the requested amendments should not be influential.[21]

24. The applicant submits that the opponent has failed to properly explain why it has sought to amend the SGP at this late stage in proceedings, and that the opponent's assertion that the amendments are being sought "for consistency with the filed evidence" does not constitute a satisfactory explanation for the delay, particularly given that evidence in reply was filed in February 2020.[22]

25. As outlined above, I consider that the prejudice to the applicant in light of the proposed amendments was only minimal, as all the added material was either discussed by Professor Currie in the EIS, or raised by Professor Currie directly in response to the EIA. I also consider the inclusion of this material in the SGP to be in the public's interest as a correct determination of the opposition is one based on the issues properly raised in the opposition proceedings. The other important factor considered in the *CSL decision* relates to the timing of the amendment request and the reasonableness of the explanation of the delay.

26. In relation to the timing, what is particularly concerning is the delay in amending the SGP after the conclusion of the EIS evidentiary period. The SGP was proposed to be amended on 31 August 2020, which was nearly a year later than the EIS was filed on 6 September 2019. The opponent seeks to explain this delay by submitting that responsibility of the opposition was transferred to Pearce IP at the end of June 2020, and the filing of the

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[16] Currie-1 at [35]-[40].
[17] Currie-2 at [34]-[41] and [67].
[18] Opponent's Correspondence dated 6 October 2020.
[19] Opponent's Correspondence dated 6 October 2020.
[20] Opponent's Correspondence dated 6 October 2020.
[21] Opponent's Correspondence dated 6 October 2020.
[22] Applicant's Correspondence dated 15 September 2020.

amended SGP on 30 August 2020, reflects the view that was taken that in light of the matters that had been addressed in the parties' evidence, the SGP should be amended to reflect the issues raised in the evidence.[23] While this delay was clearly not ideal, in my view, given the nature of the particulars to be added and their clear presence in the evidence, any undue prejudice to the applicant was nominal, and the inclusion of the material in the SGP as proposed to be amended clarifying the case to be answered is in the public's interest, and the lengthy delay in amending the SGP is of less weight. I consider it appropriate to formally allow the amendments to the SGP dated 30 August 2020. In any event, I note that the parties have addressed these particulars as part of their cases.

The specification

27. The opposed application claims priority from four priority document, US61/734,256 filed on 6 December 2012, US61/758,624 filed on 30 January 2013, US61/761,046 filed on 5 February 2013 and US61/794,422 filed on 15 March 2013, the contents of which are incorporated into the present specification by reference. The specification as accepted comprises description pages from 1 to 63, claims from pages 64-66, drawings pages 1/7-7/7, and a sequence listing from page 1 to page 23. There are 18 claims, including two independent claims (claims 1 and 2). The claims in full appear in the ANNEX at the end of this decision.

What is the invention as described?

28. Before commencing to construe the specification, I note what Middleton J said in *Eli Lilly and Company Limited v Apotex Pty Ltd*:[24]

> "It is well settled that the Court should, from the outset, approach the task of patent construction with a generous measure of common sense. The Court must place itself in the position of a person skilled in the relevant art, being the subject matter of the patent. From this perspective, the patent is to be read as a whole, in the context of the specification and in light of the prevailing common general knowledge and state of the relevant art at the priority date."

The background to the invention

29. The application is titled "CRISPR-based Genome Modification and Regulation".

30. The Field of the Invention relates to targeted genome modification, in particular, RNA-guided endonucleases or fusion proteins comprising CRISPR/Cas-like protein and methods of using said proteins to modify or regulate targeted chromosomal sequences.[25]

31. The Background of the Invention discusses that current methods for targeted genome modification rely on engineered nuclease enzymes such as zinc finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs), where each new genomic target requires the design of a new ZFN or TALEN comprising a novel sequence-specific DNA-

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[23] Opponent's Correspondence dated 27 October 2020.
[24] [2013] FCA 214; 100 IPR 451 at [139].
[25] Specification at [0001].

binding module. Such custom designed nucleases tend to be costly and time consuming to prepare, and they can mediate off-target cleavages.[26]

Summary of Invention

32. The invention is broadly summarised as "an isolated RNA-guided endonuclease, wherein the endonuclease comprises at least one nuclear localization signal, at least one nuclease domain, and at least one domain that interacts with a guide RNA to target the endonuclease to a specific nucleotide sequence for cleavage.[27] A further aspect of the invention encompasses a method for modifying a chromosomal sequence in a eukaryotic cell comprising introducing into a eukaryotic cell (i) at least one RNA-guided endonuclease comprising at least one nuclear localisation signal (NLS), (ii) at least one guide RNA, and, optionally, (iii) at least one donor polynucleotide comprising a donor sequence.[28] The RNA-guided endonuclease interacts with specific guide RNAs, each of which directs the endonuclease to a specific targeted site, at which site the RNA-guided endonuclease introduces a double-stranded break that can be repaired by a DNA repair process such that the chromosomal sequence is modified.[29] The methods disclosed can be used to target and modify specific chromosomal sequences.[30]

33. Another aspect of the present invention is a method for modifying a chromosomal sequence in a eukaryotic cell. The method comprises introducing into a eukaryotic cell (i) at least one RNA-guided endonuclease comprising at least one NLS, (ii) at least one guide RNA or DNA encoding at least one guide RNA, and, optionally, (iii) at least one donor polynucleotide comprising a donor sequence. The method further comprises culturing the cell such that each guide RNA directs an RNA-guided endonuclease to a targeted site in the chromosomal sequence where the RNA-guided endonuclease introduces a double stranded break in the targeted site, and the double-stranded break is repaired by a DNA repair process such that the chromosomal sequence is modified.[31] In other embodiments, the method can comprise introducing two RNA-guided endonucleases and two guide RNAs into a cell, wherein the RNA-guided endonucleases introduce two double-stranded breaks in the chromosomal sequence.[32]

Examples

34. The specification provides nine examples which I will discuss below.

35. Example 1 involves the modification of Cas9 gene for mammalian expression. In this example, a Cas9 gene from *Streptococcus pyogenes* strain MGAS15252 (Accession number YP_005388840.1) was optimised with *Homo sapiens* codon preference to enhance its translation in mammalian cells. The *Cas9* gene also was modified by adding a NLS PKKKRKV (SEQ ID NO:1) at the C terminus for targeting the protein into the nuclei of mammalian cells.[33]

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[26] Specification at [0002].
[27] Specification at [0004] and [0014].
[28] Specification at [0005].
[29] Specification at [0014].
[30] Specification at [0014].
[31] Specification at [0063].
[32] Specification at [0065].
[33] Specification at [0142].

36. Example 2 describes the use of the adeno-associated virus integration site (AAVS1) locus as a target for Cas9-mediated human genome modification. Three Cas9 guide RNAs were designed. The first was a 42 nucleotide RNA (crRNA) comprising (5' to 3') a target recognition sequence and protospacer sequence. The second was an 85 nucleotide RNA (tracrRNA) comprising 5' sequence with complementarity to the 3' sequence of the crRNA and additional hairpin sequence. The third was a chimeric RNA comprising nucleotides 1-32 of the crRNA, a GAAA loop, and nucleotides 19-45 of the tracrRNA.[34]

37. Example 3 involves the preparation of donor polynucleotide to monitor genome modification where targeted integration of a GFP protein into the N terminus of PPP1R12C was used to monitor Cas9-mediated genome modification. The prepared AAVS1-GFP DNA donor contained a 5' (1185bp) AAVS1 locus homologous arm, an RNA splicing receptor, a turbo GFP coding sequence, a 3' transcription terminator, and a 3' (1217bp) AAVS1 locus homologous arm. Targeted gene integration will result in a fusion protein between the first 107 amino acids of the PPP1R12C and the turbo GFP.[35]

38. Example 4 describes Cas9-mediated targeted integration of human K562 cells. Table 7 which is extracted below, describes the transfection of K562 cells with four different treatments (A-D). Fluorescence-activated cell sorting (FACS) was performed 4 days after transfection, and the specification concludes that the percent GFP detected in each of the four experimental treatments (A-D) was greater than in the control treatments (E, F), confirming integration of the donor sequence and expression of the fusion protein.[36]

Table 7. Transfection Treatments

Treatment	Modified Cas9	Guide RNA	Donor sequence
A	Cas9 mRNA transcribed with Anti-Reverse Cap Analog (10 µg)	pre-annealed crRNA-tracrRNA duplex (0.3 nmol)	AAVS1-GFP plasmid DNA (10 µg)
B	Cas9 mRNA transcribed with Anti-Reverse Cap Analog (10 µg)	chimeric RNA (0.3 nmol)	AAVS1-GFP plasmid DNA (10 µg)
C	Cas9 mRNA capped via post-transcription capping reaction (10 µg)	chimeric RNA (0.3 nmol)	AAVS1-GFP plasmid DNA (10 µg)
D	Cas9 plasmid DNA (10 µg)	U6-chimeric RNA plasmid DNA (5µg)	AAVS1-GFP plasmid DNA (10 µg)
E	None	None	AAVS1-GFP plasmid DNA (10 µg)

[34] Specification at [0145].
[35] Specification at [0147].
[36] Specification at [0149].

F	None	None	None

39. Example 5 describes the PCR confirmation of targeted integration, where genomic DNA was extracted from transfected cells 12 days after transfection, and amplified with a forward primer located outside the 5' homologous arm of the AAVS1-GFP plasmid donor and a reverse primer located at the 5' region of the GFP, with an expected fragment size of 1388bp.[37] Cells transfected with treatment A displayed a PCR product of the expected size (Lane A in Figure 5).[38]

40. Examples 6 and 7 describe a Cas9-based genome editing experiment in mouse embryos, and Examples 8 and 9 describe a Cas9-based genome editing experiment in rat embryos. However, Examples 6-9 appear to only be proposed experiments with no results given as to whether there was any successful cleavage of genomic DNA.[39]

The Person Skilled in the Art

41. The person skilled in the art (PSA) was considered in *Root Quality Pty Ltd v Root Control Technologies Pty Ltd*:[40]

> "He is the person to whom the patent is addressed and who must construe it. He is the person whose knowledge will determine whether a patent is novel. He is the person who will judge whether a patent is obvious."

42. However, the PSA is not a real person, but an artificial construct that is used as a tool of analysis which is used to make the determination:

> "The notional person is not an avatar for expert witnesses whose testimony is accepted by the court. It is a pale shadow of a real person – a tool of analysis which guides the court in determining, by reference to expert and other evidence, whether an invention as claimed does not involve an inventive step."[41]

43. The opponent submits that in the present case, the PSA is a person who was involved in the field of genome editing, i.e. a researcher who performed targeted modification of genome sequences to, for example, investigate the function of the genes.[42] The applicant is in broad agreement with this statement of the PSA.[43]

44. The opponent submits that Professor Currie is eminently qualified to give evidence in this opposition, as he is a molecular geneticist who has used methods of targeted modification to manipulate genes in a zebrafish model, particularly using ZFN genome editing technology.[44] On the other hand, the opponent questions the expertise of the applicant's expert, Professor Cannon, submitting that Professor Cannon has only limited expertise in

[37] Specification at [0150].
[38] Specification at [0151].
[39] Specification at [0152]-[0159].
[40] [2000] FCA 980; 49 IPR 225 at [70].
[41] *AstraZeneca AB v Apotex Pty Ltd* [2015] HCA 30; 257 CLR 356 at [23].
[42] Opponent's Written Submissions at [23].
[43] Applicant's Written Submissions at [56].
[44] Opponent's Written Submissions at [24].

relation to targeted genome manipulation before the earliest priority date.[45] Professor Currie provides evidence that Professor Cannon had only published one paper that involved the use of gene editing technology (ZFN technology) before the priority date.[46]

45. The applicant responds by stating that the opponent's criticism of Professor Cannon is unwarranted, submitting that Professor Cannon's paper on ZFNs in 2010, was a seminal paper published in *Nature Biotechnology*[47] describing the use of ZFNs to disrupt the CCR5 gene.[48] The applicant submits that Professor Cannon's standing in the field was recognised by her invitation as a speaker at a premier biannual meeting in the field of genome engineering.[49]

46. The applicant further seeks to cast doubt on the reliability of Professor Currie's evidence as his various propositions in relation to the disclosure in the examples of the priority documents are entirely inconsistent with his evidence in relation to inventive step. For example, it argued that Professor Currie's assertions that the experiments provided in the Jinek paper which did not even involve eukaryotic cells, "provided all the information necessary to modify eukaryotic genes with the CRISPR/Cas9 system"[50] stands in stark contrast with his assertion that the experimental results in the priority document would not enable the person skilled in the art to perform the invention.[51]

47. Despite the parties criticisms of their opposing experts, I consider both Professor Currie and Professor Cannon have the relevant experience to be considered as representative of the hypothetical PSA in the field of genome editing. As such, I will weigh the evidence of the declarants in the usual manner. The applicant's accusation that Professor Currie's evidence is impermissibly tainted by hindsight, will be explored under the relevant sections of this decision.

Construction

48. The correct approach to the construction of claims was discussed by Bennet J in *H Lundbeck A/S v Alphapharm Pty Ltd*:[52]

> "the words in a claim should be read through the eyes of the skilled addressee in the context in which they appear … while the claims define the monopoly claimed in the words of the patentee's choosing, the specification should be read as a whole … it is not permissible to read into a claim an additional integer or limitation to vary or qualify the claim by reference to the body of the specification … terms in the claim which are unclear may be defined or clarified by reference to the body of the specification."

[45] Opponent's Written Submissions at [25].
[46] Currie-2 at [5].
[47] Holt et al., Nature Biotechnology, 2010, Vol. 28, pages 839-847 (Exhibit 7 to Cannon).
[48] Applicant's Written Submissions at [59].
[49] Applicant's Written Submissions at [60].
[50] Currie-1 at [60].
[51] Applicant's Submissions at [88].
[52] [2009] FCAFC 70; 81 IPR 228 at [118]-[120].

Construction of claim 1

49. Claim 1 is the first independent claim. It reads:

> "A method for modifying a chromosomal sequence in a eukaryotic cell by integrating a donor sequence, the method comprising:
> a) introducing into the eukaryotic cell
> (i) at least one RNA-guided endonuclease comprising at least one nuclear localization signal or nucleic acid encoding at least one RNA-guided endonuclease comprising at least one nuclear localization signal, wherein the at least one RNA-guided endonuclease is a clustered regularly interspersed short palindromic repeat (CRISPR)/CRISPR-associated (Cas)(CRISPR/Cas) type II system protein and the CRISPR/Cas type II system protein is a Cas9 protein,
> (ii) at least one guide RNA or DNA encoding at least one guide RNA, and
> (iii) a donor polynucleotide comprising the donor sequence; and
> b) culturing the eukaryotic cell such that each guide RNA guides an RNA-guided endonuclease to a target site in the chromosomal sequence, the RNA-guided endonuclease introduces a double-stranded break at the target site, and the double-stranded break is repaired by a DNA repair process such that the chromosomal sequence is modified by insertion or substitution of the donor sequence into the chromosomal sequence; wherein
> the target site in the chromosomal sequence is immediately followed by a protospacer adjacent motif (PAM),
> the method does not comprise a process for modifying the germ line genetic identity of a human being and, wherein
> the method does not comprise a method for treatment of the human or animal body by surgery or therapy."

Cas9 protein

50. While the specification fails to provide an explicit definition of a Cas9 protein, the specification states that in general, a Cas9 protein comprises at least two nuclease (i.e. DNAse) domains,[53] which can include a RuvC-like nuclease domain and a HNH-like nuclease domain.[54] The only exemplified Cas9 protein was expressed from a Cas9 gene from *Streptococcus pyogenes* strain MGAS15252 which was optimised with *Homo sapiens* codon preference to enhance its translation in mammalian cells.[55]

51. While the specification includes a number of references to endonucleases *derived* from a Cas9 protein,[56] there is no dictionary definition in the specification that limits the Cas9 protein to being a Cas9 *derived* protein. Furthermore, other parts of the specification disclose that suitable CRISPR/Cas proteins include "Cas9" proteins as opposed to "Cas9 derived" proteins.[57] As the claims define a "Cas9" protein and not a "Cas9 derived" protein, I consider that Cas9 *modified* proteins fall within the scope of a Cas9 protein. I see no reason to implicitly limit the scope of a Cas9 protein to a Cas9 modified protein. This construction is consistent with the evidence of Professor Currie who states "[a]s the Cas9

[53] Specification at [0022].
[54] Specification at [0022].
[55] Specification at Example 1.
[56] Specification at [0004], [0005], [0018] and [0021].
[57] Specification at [0017].

protein is the final description in part (a)(i) and is not associated with any further modifying language, I take this to mean that part (a)(i) is a wild-type Cas9 protein."[58] It follows that the scope of "Cas 9" protein includes wild-type Cas9 proteins as well as modified Cas9 proteins or Cas9-like proteins, which could include fusion proteins or genes that are codon optimised for efficient translation into protein in the eukaryotic cell.

Nuclear localization signal

52. The claims define that the Cas9 protein also needs to comprise at least one NLS. The specification states that in general, an NLS comprises a stretch of basic amino acids.[59] The specification also describes the NLS as being a monopartite sequence, such as PKKKRKV (SEQ ID NO:1) or PKKKRRV (SEQ ID NO:2), or a bipartite sequence, and can be located at the N-terminus, the C-terminal, or in an internal location of the RNA-guided endonuclease.[60]

53. The specification states that a NLS permits entry of the endonuclease into the nuclei of eukaryotic cells.[61] Professor Cannon reads this passage as "describing a Cas9 protein that includes an NLS, irrespective of whether the Cas9 protein is utilised in its wild-type form and also happens to fortuitously include a eukaryotic NLS within its sequence, or it is a Cas9 protein that is modified in some way (*e.g.*, via insertion of an NLS at the C- or N-terminus)."[62]

54. The opponent submits that the evidence of Professor Currie clearly demonstrates that Cas9 from *S. pyogenes* includes endogenous NLSs.[63] Currie-1 provides evidence that:

> "the Cas9 protein from *S. pyogenes* has two monopartite NLSs with scores associated with localization to the nucleus, and four bipartite NLSs with scores associated with localisation to the nucleus, and four bipartite NLSs with scores associated with localization to both the nucleus and the cytoplasm."[64]

55. However, Professor Currie appears to concede that the Cas9 protein from *S. pyogenes* does not carry a *bona fide* "classical" NLS such as one of the NLSs described in paragraph [0023] of the opposed application,[65] but may include a "cryptic" NLS which while having a sequence different than the sequence motif of a classical NLS, can nevertheless be recognized by the nucleus transport machinery.[66] I consider the NLSs described in paragraph [0023] of the opposed application, to merely be preferred embodiments of different types of NLSs, as this paragraph uses words such as "[i]n general", [f]or example", and "in another embodiment." There is no such limitation in the language of the claims requiring the NLS to be a *bona fide* or "classical" NLS using the words of Professor Currie. In my view, the only implied limitation on the NLS defined in the claims is that the NLS must be capable of permitting entry of the endonuclease into the nucleus of eukaryotic cells. This construction is also consistent with the evidence of Professor Cannon who

[58] Currie-1 at [143].
[59] Specification at [0023].
[60] Specification at [0023].
[61] Specification at [0016].
[62] Cannon at [227].
[63] Opponent's Written Submissions at [161].
[64] Currie-1 at [143].
[65] Currie-1 at [143].
[66] Currie-1 at [143].

submits that a wild-type Cas9 could fortuitously include a eukaryotic NLS within its sequence, and the evidence of Professor Currie who references Hu et al (2018)[67] which demonstrates that *S pyogenes* Cas9, without an added NLS, successfully induced editing of the zebrafish genome.[68] Therefore the term "NLS" is construed as including a wild-type Cas9 which includes a "cryptic" NLS that has been demonstrated to permit entry of the endonuclease into the nuclei of eukaryotic cells.

Guide RNA

56. The specification provides that the guide RNA interacts with the RNA-guided endonuclease to direct the endonuclease to a specific target site, at which the 5' end of guide RNA base pairs with a specific protospacer sequence in the chromosomal sequence.[69] Each guide RNA comprises three regions: a first region at the 5' end that is complementary to the target site in the chromosomal sequence, a second internal region that forms a stem loop structure, and a third 3' region that remains essentially single-stranded.[70] The first region of each guide RNA is different such that each guide RNA guides a fusion protein to a specific target site, whereas the second and third regions of each guide RNA can be the same in all guide RNAs.[71]

57. The first region (at the 5' end) of the guide RNA is complementary to the sequence (i.e., protospacer sequence) at the target site in the chromosomal sequence such that the first region of the guide RNA can base pair with the target site.[72] The second region of the guide RNA forms a secondary structure, which in some embodiments comprises a stem (or hairpin) and a loop.[73] The third region of the guide RNA comprises a 3' end that remains essentially single stranded such that the third region has no complementarity to any chromosomal sequence in the cell of interest and has no complementarity to the rest of the guide RNA.[74]

Protospacer adjacent motif (PAM)

58. Examples of PAMs include, but are not limited to, NGG, NGGNG, NNAGAAW (wherein N is defined as any nucleotide and W is defined as either A or T).[75]

Modifying a chromosomal sequence in a eukaryotic cell by integrating a donor sequence

59. The preamble to claim 1 defines "[a] method *for* modifying a chromosomal sequence in a eukaryotic cell *by* integrating a donor sequence." There was much discussion at the hearing regarding how this preamble impacts the scope of claim 1.

60. The Examiner's Manual of Practice and Procedure (EMPP) states at 2.11.2.3.3:

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[67] Hu, P. et al, G3:Genes, Genomes, Genetics, March 2018, Vol. 8, pages 823-831 (Exhibit PDC-35).
[68] Currie-2 at [98].
[69] Specification at [0070].
[70] Specification at [0071].
[71] Specification at [0071].
[72] Specification at [0072] and [0081].
[73] Specification at [0073].
[74] Specification at [0074].
[75] Specification at [0081].

> "In general, method or process claims using words of purpose are construed as being restricted to that purpose as a result of process steps in the method imparting that restriction. For example, a claim defining … "A method for producing X…." is limited to a method that would result in the production of X. Note, however, that there may be exceptions (see *CSL Limited v Pharmacia & Upjohn* AB [2000] APO 58) and that construction of method or process claims may vary depending on the facts of the case."

61. Following the general guidance in the EMPP, claim 1 would be construed as a method that would actually as a matter of fact result in the modification of a chromosomal sequence in a eukaryotic cell by integrating a donor sequence, rather than the method merely being "suitable for" modifying a chromosomal sequence in a eukaryotic cell by integrating a donor sequence, without *actually* doing so. I see no reason to depart from this general construction.

62. At the hearing, there was some dispute about whether the scope of the claims extended to integration of the donor sequence anywhere in the eukaryote chromosome or whether the scope of the claims was limited to "site specific" integration of the donor sequence at the target site. The opponent submitted that the preamble to claim 1 only states that the donor sequence needs to be *integrated* (and not site specifically integrated) into the chromosome, and that the culturing step b) does not use the language of targeted integration. The applicant submitted that while the claims do not use the explicit language of *targeted integration*, such integration is implied by reading the claim in context, specifically part b) which limits the claims to having a Cas9 guided by the guide RNA to a *target site* in the chromosomal sequence and the Cas9 introducing a double strand break at the *target site* which is repaired by a DNA repair process such that the chromosomal sequence is modified by *insertion or substitution* of the donor sequence into the chromosomal sequence. I agree with the applicant, and consider that the claims are limited to *site specific integration* as the Cas9 is guided by the guide RNA to the target site which is immediately followed by a PAM, the Cas9 then introduces a double strand break at the target site, and the chromosomal sequence is modified by insertion or substitution of the donor sequence into the chromosomal sequence, which by the nature of how the CRISPR mechanism works, can only be *site specific* integration of the donor sequence at the target site.

63. A key issue in this decision related to the experimental methodology used in the opposed specification to establish that integration of the donor sequence had occurred. The opposed specification states that "[t]he percent GFP detected in each of the four experimental treatments (A-D) was greater than in control treatments (E, F), confirming *integration* [emphasis added] of the donor sequence and expression of the fusion protein."[76]

64. The opponent's argument is that the PCR results of Example 5 do not support a conclusion that site specific integration of the GFP sequence has occurred in test samples B-D, which utilised chimeric guide RNA. The opponent relies on the evidence of Professor Currie who submits that he cannot conclude that there has been any successful integration of the GFP on the basis of Example 4 alone, as the opposed specification does not disclose a statistically significant increase in fluorescence measured in test samples A to D when compared to the control.[77] Professor Currie further states that because Example 4 only detects fluorescence, it is not possible to know on the basis of Example 4 alone if any GFP

[76] Specification at [0149].
[77] Currie-1 at [122].

has been integrated in the target locus of the cell as opposed to, for example, integration into a non-target site.[78]

65. The applicant submits that the skilled person would understand from the experimental results in the opposed specification that site specific integration had occurred.[79] Professor Cannon's evidence states that when considering the FACS results presented in Example 4, the inclusion of a matched CRISPR-Cas9 targeting the same locus as the homology donor increased the level of GFP expression above the background in all 4 experimental arms (A-D) in Figure 4.[80] Professor Cannon reviews Moehle et al. (Exhibit 23) in his evidence and concludes that in 2012, the skilled person understood that using GFP flow cytometry analysis and comparing the rate of GFP+ cells in "donor only" treated populations versus "targeted nuclease plus donor" populations was an accepted way to demonstrate site specific integration.[81] In relation to the present case, Professor Cannon submits that all 4 experimental arms (A-D) in Figure 4 give a net positive value,[82] which demonstrates that all the samples in Figure 4 containing CRISPR-Cas9 reagents show a strong increase compared to the background signal obtained from Treatment E.[83] This lead Professor Cannon to conclude that the skilled person would, therefore, have found the results presented in Example 4 to be a *powerful indication* [emphasis added] that the method described would have had indeed resulted in site-specific integration of the GFP cassette into the targeted PPP1R12C locus.[84]

66. In response, Professor Currie submits that the publications referred to by Professor Cannon (including Moehle et al) to support her view that flow cytometry can be used confirm site specific integration of a reporter gene, all used methods other than flow cytometry to confirm site specific integration.[85] Professor Currie also raises the possibility that flow cytometry may well confirm that a sequence has been taken up into the cell, but it may be in the cell in any context such as randomly inserted or episomally inserted.[86] Professor Cannon responds to this criticism by submitting that the FACS experiment in Example 4 allows for such GFP signals that did not rely on HDR-mediated site-specific insertion by inclusion of the donor only control (Treatment E) which establishes a background level of fluorescence to compare the four experimental treatments (Treatments A-D) against.[87]

67. In my view, the evidence provides competing scientific opinion on whether the test methods disclosed in Example 4 establish that site specific integration of the donor sequence has occurred. While it is arguable that the data provided in Example 4 cannot *prove* that site specific integration has occurred, in my view there is insufficient evidence to establish that the methods disclosed in Example 4 *would not* be able to determine whether site specific integration has occurred. Professor Cannon's evidence discusses that there are disadvantages with the "in-out PCR" method described in Example 5, including sequestration of the GFP primer by unintegrated plasmid donors resulting in a lower than

[78] Currie-1 at [122].
[79] Applicant's Written Submissions at [92].
[80] Cannon at [43] and [44].
[81] Cannon at [33]-[36].
[82] Applicant's Written Submissions at [99]; Cannon at [43] and [44].
[83] Applicant's Written Submissions at [99]; Cannon at [50] and [51].
[84] Cannon at [52].
[85] Currie-2 at [15]-[18].
[86] Currie-2 at [11].
[87] Cannon at [41]-[44].

expected detection of PCR product,[88] and reduced sensitivity in interrogating the AAVS1 locus using in-out PCR producing a "non zero false negative rate".[89] While this issue is finely balanced, I consider that the specification stating in Example 4 that there was "integration" in treatments A-D, the fact that the experiment in Example 5 is titled as a "confirmation" experiment, and the fact that Professor Cannon has provided evidence on the difficulties with the in-out PCR in Example 5, weighs towards Example 4 alone demonstrating that site specific integration has occurred in treatments A-D. I further note that another scientific publication in evidence, Mali et al (PDC-7), shows successful site specific integration in mammalian cells using guide RNAs comprising crRNA tracrRNA fusion transcripts, which deliver the guide RNA in a manner similar to treatments B and C of the opposed application, rather than the pre-annealed guide RNA in treatment A. Therefore, I will proceed with the rest of this decision based on this conclusion.

Clarity

68. It is a requirement of section 40(3) of the *Patents Act* that the claims must be clear. This requirement is understood to be satisfied if a person could ascertain "whether or not what he proposes to do falls within the ambit of the claim".[90]

69. As noted in *Flexible Steel Lacing Company v Beltreco Ltd*[91] cited with approval in *Austal Ships Sales Pty Ltd v Stena Rederi Aktiebolag*[92]:

> "The consideration is whether, on any reasonable view, the claim has meaning. In determining this, the expression in question must be understood in a practical, common sense manner."

70. The opponent submits that claims 1 and 2 lack clarity because it is unclear whether the claims include any wild-type Cas9 protein that has a "cryptic" NLS, or only include modified Cas9 proteins that have been modified to include a classical (exogenous) NLS.[93] However, as discussed previously, I have construed "Cas9 proteins" as including wild-type Cas9 proteins as well as modified Cas9 proteins or Cas9-like proteins, which could include fusion proteins or genes that are codon optimised for efficient translation into protein in the eukaryotic cell.

71. As a result, I consider the scope of claims 1 and 2 to be clear.

72. The opponent further submits that claim 18 lacks clarity as claim 18 defines the guide RNA as "chemically synthesised" but claim 12 which claim 18 depends (in part) defines a limitation that the guide RNA is encoded by a sequence in a DNA vector, which does not encompass chemically synthesised guide RNA (as chemically synthesised RNA is not encoded by a sequence in a DNA vector).[94]

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[88] Cannon at [57].
[89] Cannon at [58].
[90] *Monsanto Co v Commissioner of Patents* (1974) 48 ALJR 59.
[91] [2000] FCA 890; (2000) IPR 331.
[92] [2008] FCAFC 121; (2008) 77 IPR 229.
[93] Opponent's Written Submissions at [51] and [52].
[94] Opponent's Written Submissions at [53].

73. Claim 18 is appended to claims 1-17, and only claim 12 defines guide RNA that is not "chemically synthesised". Any confusion arising from this appendancy is easily resolved. I consider that claim 18 would be understood as only appended to claims 1-11 and 13-17. As a result, I consider the scope of claim 18 to be clear. However, the applicant may like to consider amending the claim to make the meaning explicit.

Clear enough and complete enough disclosure

74. Paragraph 40(2)(a) as amended by the *Raising the Bar Act* requires that the claimed invention be described in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art.

75. It is clear that this provision requires that the PSA must be able to perform the invention across the scope of the claim without undue burden or inventive skill.[95] In *Evolva SA*[96] (***Evolva***), the Deputy Commissioner considered paragraph 40(2)(a), and having drawn guidance from European and UK decisions, adopted the following approach to assessing a clear and complete enough disclosure:

> What is the scope of the invention as claimed?
>
> What does the specification disclose to the skilled person?
>
> Does the specification provide an enabling disclosure of all the things that fall within the scope of the claims, and in particular:
>
>> Is it plausible that the invention can be worked across the full scope of the claim?
>>
>> Can the invention be performed across the full scope of the claim without undue burden?

76. This approach has subsequently been adopted by delegates of the Commissioner,[97] and while the section 40 provisions as amended by the *Raising the Bar Act* were recently considered by the Federal Court for the first time in *Encompass Corporation v InfoTrack Pty Ltd*[98], the detail of the approach to considering clear enough and complete enough disclosure was not at issue. I will adopt the Deputy Commissioner's approach to considering this ground.

77. The second limb of the enablement test is whether performing the invention across its full scope would constitute an undue burden. The concept of an undue burden was discussed in *Evolva*. Having considered UK and European authorities the Deputy Commissioner concluded:

> "My understanding of these authorities is that the emphasis in relation to undue burden has been on the nature of the work that is required by the skilled person in view of the

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[95] *Novartis AG v Johnson & Johnson Medical Limited* [2010] EWCA Civ 1039 at [74].
[96] [2017] APO 57 at [45].
[97] See, e.g. *Rimfrost AS v Aker BioMarine Antarctic AS* [2018] APO 34; *Cytec Industries Inc. v Nalco Company* [2018] APO 4; *Grant Fisher v ToolGen Incorporated* [2018] APO 65; *Gary B Cox v MacroGenics, Inc.* [2019] APO 13.
[98] [2018] FCA 421; 130 IPR 387.

guidance in the specification. To this end, one approach has been to ask whether the skilled person would be required to undertake a 'research programme' in order to perform the invention."[99]

78. A feature which is defined in broad terms will be allowable if it can be understood to be a principle of general application – which was described by Lord Hoffmann in *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* as:

> "an element of the claim which is stated in general terms. Such a claim is sufficiently enabled if one can reasonably expect the invention to work with anything that falls within the general term."[100]

What is the scope of the invention as claimed?

79. The claimed invention defines a method of modifying a chromosomal sequence in a eukaryotic cell comprising introducing into a eukaryotic cell a Cas9, a guide RNA and a donor sequence, and culturing the cell such that the guide RNA guides a Cas9 to a target site in the chromosomal sequence, the Cas9 introduces a double stranded break at the target site, and the break is repaired such that chromosomal sequence is modified by insertion or substitution of the donor sequence into the chromosomal sequence.

What does the specification disclose to the skilled person?

80. As discussed above under construction, I consider that the specification discloses to a skilled person that site specific integration of a donor sequence into a eukaryotic cell has occurred when following the defined methods, and that such integration can be verified by performing the methods disclosed in Example 4 alone, independent of Example 5.

Plausibility

81. The first limb of the test outlined in *Evolva* asks: Is it plausible that the invention can be worked across the full scope of the claim?

82. The test in *Evolva* is whether it is plausible that the invention can be worked across the full scope of the claim. The Deputy Commissioner in *Evolva* identified the question to be answered as:

> "whether it is plausible that polypeptides which have as low as 90% identity would be capable of catalysing the defined glycosylation reaction."[101]

83. After considering what was known about conservative substitutions and the binding domain of the proteins, the Deputy Commissioner concluded:

> "I can see no apparent reason why the skilled person would not consider it plausible that functional variants to a level of at least 90% could be identified and would be useful in the process defined."[102]

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[99] *Evolva* at [33].
[100] [2005] RPC 169 at [112].
[101] *Evolva* at [59].
[102] *Evolva* at [62].

84. The opponent submits that each of the claims on the face of the specification properly construed, include embodiments that Professor Currie does not consider would plausibly achieve targeted genomic modification, and there is no disclosure in the opposed application of how those embodiments could be made to achieve that result.[103]

85. In response to the opponent's submission and the evidence of Professor Currie, it is important to note that the Deputy Commissioner in *Evolva* was not saying that *every* possible variant of greater than 90% identity would have to achieve the functional outcome. Similarly, by analogy here, the use of every possible combination of Cas9, guide RNA and donor polynucleotide does not need to result in targeted chromosomal integration in a eukaryotic cell. Applying *Evolva* to the present case, I construe the technical question as: Is it plausible that the CRISPR-Cas9 method defined in claim 1 would result in the modification of a chromosomal sequence in a eukaryotic cell by integrating a donor sequence? In my view, the answer to this question is necessarily yes, as it is not even in dispute between the parties that targeted integration of the donor sequence is achieved in at least treatment A. Furthermore, as discussed above, I consider that a PSA would consider that treatments B-D also result in the integration of the donor sequence in the target chromosome.

Undue burden

86. The second limb of the test outlined in *Evolva* asks: Can the invention be performed across the full scope of the claim without undue burden?

87. The consideration of what constitutes an undue burden is necessarily dependent upon the nature of the technology, and factors relevant to the consideration include the level of predictability in the art and the level of guidance in the specification.[104]

88. The opponent submits that the claims define a result to be achieved, namely, insertion of a donor sequence into a target chromosomal sequence, but the specification provides insufficient disclosure to enable a PSA to produce the defined result based on the broadly defined elements without undue burden and/or inventive skill.[105] For example, on the face of the opposed application, there is a level of uncertainty and lack of predictability about which embodiments will achieve targeted eukaryotic genome modification, and there is no guidance on how to proceed in the face of failure.[106] However, this argument is predicated on the fact that there was no targeted chromosomal integration of the donor sequence in treatments B-D in Example 5 which I have considered previously not to be the case.

89. The opponent further submits that the method claims in the opposed application are not limited to using Cas9 or a guide RNA from any particular bacterial species,[107] and there is nothing in the opposed specification informing the reader that the second and third regions of the guide RNA in fact need to be specific sequences that are compatible with the bacterial species from which the Cas9 protein is derived.[108] The opponent cites the

[103] Opponent's Written Submissions at [270].
[104] *Evolva* at [34] and [35].
[105] Opponent's Written Submissions at [266].
[106] Opponent's Written Submissions at [267].
[107] Opponent's Written Submissions at [208].
[108] Opponent's Written Submissions at [209].

evidence of Professor Currie as evidence that Cas9 from one bacterial species does not efficiently cleave targeting DNA when the tracrRNA is derived from a different bacteria species. Currie-1 at [60] states:

> "When I read D1 [Jinek paper], I **learned that, as explained on page 818, functional and targeting of sequences requires the Cas9 and tracrRNA portion of the guide RNA to be from related species** [emphasis added]. This means that Cas9 derived from different species of bacteria do not interact with all tracrRNA sequences. D1 shows in Supplemental Figure 11 that Cas9 from one bacteria species either does not efficiently, cleave targeting DNA when the tracrRNA is derived from a different bacteria species."

90. The applicant does not appear to directly address this submission. However, Professor Cannon provided evidence that her knowledge of the CRISPR-Cas9 system at 6 December 2012 included:

    - Cas9 orthologues were found in multiple species and the PAM and crRNA sequence differed between species, and
    - A Cas9 enzyme obtained from one organism would not cleave DNA efficiently, if at all, if paired with a crRNA/tracrRNA molecule from another organism.[109]

91. The description discloses integration of a donor sequence in treatments A-D, which includes using pre-annealed crRNA-tracrRNA (Treatment A), chimeric RNA (Treatments B and C) and chimeric RNA plasmid DNA (Treatment D). I consider that a person skilled in the art would be able to perform the experiment outlined in Example 4 to determine whether there was in fact, integration of a donor sequence at the target sequence, and the person skilled in the art would be able to perform those experiments without undue burden. As noted by the applicant, the claims exclude guide RNAs, donor sequences, cleavage sites or Cas9 proteins which would *not* result in integration of the donor sequence.[110] Therefore, in order to work the invention over the full scope of the claims, I consider that the skilled addressee would simply have to test the particular combination of guide RNAs, donor sequences, and Cas9 proteins, and perform the experiment outlined in Example 4 to test whether integration has occurred.

92. Given that the opposed specification discloses that the second and third regions of each guide RNA can be the same in all guide RNAs,[111] that the first region of each guide RNA is adjusted depending on the target site, and the evidence suggests that a person skilled in the art would know that a Cas9 enzyme obtained from one organism would not cleave DNA efficiently if paired with a crRNA/tracrRNA molecule from another organism, I consider that it would be predictable which combinations of components would be likely to result in integration of the donor sequence. In other words, I do not consider that such experimentation would amount to a research programme.

93. In summary, I consider that the claimed invention is described in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art.

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[109] Cannon at [23].
[110] Applicant's Written Submissions at [240].
[111] Specification at [0071].

Priority

94. The priority date of a claim is determined by section 43 of the *Patents Act* which states that:

> (1) Each claim of a specification must have a priority date.
> (2) The priority date of a claim is:
> (a) if subsection (2A) applies to the claim –the date determined under the regulations; or
> (b) otherwise—the date of filing of the specification.
> (2A) This subsection applies to a claim if:
> (a) prescribed circumstances apply in relation to the invention defined in the claim; and
> (c) a prescribed document discloses … the invention in the claim in a manner that is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art.

95. For divisional applications, the priority date is determined by regulations 3.12 and 3.13D of the *Patents Regulations*.

96. Regulation 3.12(2) states that:

> "if more than one of regulations 3.13A to 3.13E applies to a single claim, the priority date of the claim, for paragraph 43(2)(a) of the Act, is the earliest of the dates that is determined by those regulations."

97. Regulation 3.13D determines the priority date for a divisional application filed prior to grant of a patent. The opposed application (2018229489) was a divisional application filed on 13 September 2018, which was prior to the grant of the parent application (2017204031) on 27 September 2018. Similarly, 2017204031 was also a divisional application filed on 15 June 2017, which was prior to the grant of its parent application (2013355214).

98. Regulation 3.13D states that, for a divisional application filed prior to grant of a patent, if the earlier (or parent) specification mentioned in section 79B(1) of the *Patents Act* **clearly discloses** [emphasis added] the invention of the claim in the divisional application,[112] the priority date is the priority date that the claim would have had if the claim was in the earlier specification.[113] Therefore the priority date for the claims of the opposed application is the same as the priority date that the claims would have had if the claims were in the grandparent specification (2013355214).

99. However, the 2013355214 specification claimed a priority date of 6 December 2012, which was the filing date of US61/734,256, the first of the four basic documents related to PCT/US2013/073307. Regulation 3.13A determines the priority date for PCT applications.

100. Regulation 3.13A states that if the circumstance is that the specification containing the claim that defines the invention was filed for a PCT application, and the PCT application claims the priority of an earlier application under Article 8 of the PCT,[114] and the earlier application is a basic application that was the first application made in a Convention

[112] *Patents Regulations 1991* (Cth) reg 3.13D.
[113] *Patents Regulations 1991* (Cth) reg 3.13D(3).
[114] *Patents Regulations 1991* (Cth) reg 3.13A(2)(a)(i).

country in relation to the invention,[115] and the earlier application was made no more than 12 months before the filing date of the PCT application,[116] then the priority date is the date when the earlier application was made.[117]

101. Therefore, for each claim of the opposed application to enjoy a priority date of 6 December 2012, US61/734,256 must disclose the invention defined in that claim, in a manner that is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art.

Assessment of the priority date in light of P1-P4

P1, US61/734,256, priority date 6 December 2012
P2, US61/758,624, priority date 30 January 2013
P3, US61/761,046, priority date 5 February 2013
P4, US61/794,422, priority date 15 March 2013

102. The opponent submits that none of the claims of the opposed application are entitled to priority from any of P1, P2, P3 and P4.[118] The opponent identifies a number of features encompassed by the claims of the opposed application that it argues are not disclosed in any one of P1-P4. I will consider each of these features in turn.

No disclosure of wild-type Cas9 (all claims)

103. P1 discloses RNA-guided endonucleases that are engineered for use in eukaryotic cells.[119] P1 also discloses that the RNA-guided endonucleases are *derived* from a CRISPR system, and either *derived* from a wild type Cas9 protein(s) or fragment(s) thereof or *derived* from modified Cas9 protein(s).[120] Similarly, claim 2 of P1 defines an endonuclease *derived* from a Cas9 protein. In addition, P1 discloses modifications of the RNA-guided endonuclease including modified nuclease activity, affinity and stability, and eliminating domains of the Cas9 protein not involved in RNA-guided cleavage and fusion proteins.[121] P1 also discloses RNA-guided endonucleases that comprise at least one NLS, which permits entry of the endonuclease into the nuclei of eukaryotic cells.[122] Furthermore P1 discloses that the-Cas9-*derived* endonucleases comprise at least one NLS.[123]

104. The opponent submits that P1 does not provide a disclosure of the use of wild-type Cas9 as distinct from "engineered" Cas9 derivatives.[124] The opponent submits that because the endonuclease is described in P1 as being Cas9-*derived*, the Cas9 protein is a Cas9 protein generated from a wildtype Cas9 or modified Cas9 protein and made into something different.[125]

[115] *Patents Regulations 1991* (Cth) reg 3.13A(2)(b)(iii).
[116] *Patents Regulations 1991* (Cth) reg 3.13A(2)(b)(iii)(A).
[117] *Patents Regulations 1991* (Cth) reg 3.13A(5)(a).
[118] Opponent's Written Submissions at [189].
[119] P1 at [0003].
[120] P1 at [0005] and [0006].
[121] P1 at [0006].
[122] P1 at [0004].
[123] P1 at [0008].
[124] Opponent's Written Submissions at [195].
[125] Opponent's Written Submissions at [196]; Currie-1 at [107].

105. While it is acknowledged most references to Cas9 in P1 refer to Cas9 *modified* proteins or proteins *derived* from Cas9, all these references are only to *preferred* embodiments.[126] There is no dictionary definition in P1 which clearly states that a Cas9 protein can only be a *modified* Cas9, or a protein *derived* from Cas9. In fact, P1 discloses by reference, the wild-type Cas9 gene from *Streptococcus pyogenes* strain MGAS15252 (Accession number YP_005388840.1).[127] Professor Cannon's evidence states that the phrase "endonuclease can be derived from a Cas9 protein" would be understood to include a Cas9 which has not been modified in any way other than by addition of an NLS.[128] It is important to note here that the opposed claims define a Cas9 protein *comprising* at least one NLS. As discussed above, the term "NLS" is construed as including a wild-type Cas9 which includes a "cryptic" NLS that has been demonstrated to permit entry of the endonuclease into the nuclei of eukaryotic cells. As such it is considered that P1 discloses *both* wild-type Cas9 proteins and Cas9 proteins modified in a variety of ways.

Modifying a chromosomal sequence in an embryo (all claims)

106. The opponent argues that P1 does not include any disclosure for modifying a chromosomal sequence in an embryo, such as the method described in paragraphs [0005] and [0063] of the opposed application which were only introduced in P2.[129] Professor Currie submits that claim 1 of the opposed application should be understood to cover the production of knock out animal models, which would involve manipulation of a chromosome sequence in an embryo,[130] and manipulation of gene sequences in a non-human embryo is specifically referred to in claim 13 of the opposed application.[131] The applicant responds by submitting that the opponent fails to provide a foundation for the proposition that the skilled person would be unable to perform the claimed method in an embryo.[132]

107. Neither of the parties adduce any evidence on whether it would be undue burden on a person skilled in the art to perform the claimed methods of the invention in an embryo. However, Professor Cannon does state that:

> "by 6 December 2012, for all known cases of successful genome engineering in eukaryotic cells, *embryos* [emphasis added] or organisms using targeted nucleases, the specificity of DNA binding has been provided by wholly eukaryotic components."

108. Similarly, Professor Currie, when asked about cell culture methodologies available at and before 6 December 2012, stated that standard methods existed to introduce nucleic acids into embryos.[133] As a result, the evidence suggests that genome engineering in embryos was standard in the art at 6 December 2012, and in the absence of evidence to the contrary, I consider that a person skilled in the art upon reading P1, would be able to perform the claimed invention in an embryo without undue burden. As such it is considered that P1 discloses modifying a chromosomal sequence in an embryo.

[126] See P1 at [0005]-[0007], [0008], [0010] and [0012].
[127] P1 at [0059].
[128] Cannon at [228].
[129] Opponent's Written Submissions at [200].
[130] Currie-1 at [130].
[131] Opponent's Written Submissions at [200].
[132] Applicant's Written Submissions at [103].
[133] Currie-1 at [24].

At least one RNA-guided endonuclease (all claims)

109. The opponent submits that P1 provides no disclosure of a method using more than one RNA-guided endonuclease as covered by the claims of the opposed application, with their only being disclosure of a method using *one* RNA-guided endonuclease.[134] The applicant argues that the opponent fails to explain why the exemplification of the method using one RNA guided endonuclease provides a foundation for the proposition that the skilled person would be unable to perform the claimed method using one or more guided endonucleases.[135]

110. The parties adduced no evidence on this point. In the absence of any evidence to the contrary, I agree with the applicant's submission and see no evidence why there would be an undue burden placed on a person skilled in the art to use the guidance provided in P1 to work the method with *one* RNA-guided endonuclease and simply perform the same method with *two* or more RNA-guided endonucleases.

Features lacking due to repercussive effect of claims 5, 6 and 8

111. The opponent submits that each claim other than claim 5 of the opposed application encompasses a guide RNA that *lacks* a first region with complementarity to the target site, based on the repercussive effect of claim 5,[136] each claim other than claim 6 encompasses a guide RNA that *lacks* a region that interacts with the RNA-guided endonuclease, based on the repercussive effect of claim 6,[137] and each claim other than claim 8 encompasses a donor sequence that *lacks* sequences having substantial sequence identity to sequences flanking the target sequence, based on the repercussive effect of claim 8.[138]

112. While I consider that these features identified by the opponent are necessary for the invention to work, I do not consider that the scope of all claims other than claims 5, 6 and 8 respectively, extend to these features being *lacking*, as the evidence fails to establish that a PSA would not read such features into these claims. I consider that these features are implicit in the respective claims, as without such features the claimed invention would not work, and a construction according to which the invention will work is preferred to one according to which it may not do so.[139] As a result, I consider that there is no need to assess P1 for disclosure of these features.

Conclusion

113. In summary, I consider that the claims defined in the opposed application are entitled to the earliest priority date of 6 December 2012 afforded to them by the disclosure of P1. As such, there is no need to assess the disclosure of P2-P4.

[134] Opponent's Written Submissions at [203].
[135] Applicant's Written Submissions at [104].
[136] Opponent's Written Submissions at [213].
[137] Opponent's Written Submissions at [216].
[138] Opponent's Written Submissions at [229].
[139] See *Pfizer Pharmaceuticals v Eli Lilly* [2005] FCAFC 224.

Novelty

114. It is well established that the general test for anticipation is the reverse infringement test. The classic formulation of this test is that given by Aicken J:

> "The basic test for anticipation or want of novelty is the same as that for infringement and generally one can properly ask oneself whether the alleged anticipation would, if the patent were valid, constitute and infringement."[140]

115. This test is satisfied if the alleged anticipation discloses all the essential features of the invention claimed.[141]

116. To meet this requirement, the prior art must contain "clear and unmistakable directions to do what the patentee claims to have invented... A signpost, however clear, upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee."[142]

117. A prior disclosure will only invalidate a claim if, after having read it, the skilled addressee would, rather than could, have produced all the essential features of the claim. As stated in *Canadian General Electric Co., Ltd v Fada Radio Ltd*:[143]

> "Where the question is solely one of prior publication, it is not enough to prove that an apparatus described in an earlier specification could have been used to produce this or that result. It must also be shown that the specifications contain clear and unmistakable directions to use it."

WO 2013/176772

118. WO 2013/176772 A1 (designated **D3**) was published on 28 November 2013 and has an earliest priority date of 25 May 2012. D3 claims priority from four priority documents, US61/652,086 filed on 25 May 2012, US61/716,256 (designated the **'256 application**) filed on 19 October 2012, US61/757,640 filed on 28 January 2014 and US61/765,576 filed on 15 February 2013. The earliest priority document (US61/652,086) is not in evidence. As a result, if D3 is entitled to priority from the '256 application, D3 forms part of the prior art base for whole of contents novelty.

119. The applicant submits that the opponent has never pleaded that it relies on the whole of contents provisions of the *Patents Act*, and as a result, the applicant is unfairly prejudiced as it never had the opportunity to lead evidence directly addressing this issue, and submits it should not be open to the opponent to make submissions on this particular ground.[144] The applicant further submits that Professor Currie provides no evidence as to whether or not the claims of D3 are entitled to claim priority from the '256 application,[145] and the

[140] *Meyers Taylor Pty Ltd v Vicarr Industries Ltd* [1977] HCA 19; 137 CLR 228 at 235.
[141] *Nicaro Holdings Pty Ltd v Martin Engineering Company* [1990] FCA 40; 16 IPR 545 at 549.
[142] *The General Tire & Rubber Company v The Firestone Tyre and Rubber Company Limited* [1972] RPC 457 at [485]-[486].
[143] (1930) 47 RPC 69 at 90.
[144] Applicant's Written Submissions at [120].
[145] Applicant's Written Submissions at [121].

opponent's failure to adduce evidence is a fundamental deficiency in its newly constructed "whole of contents" novelty case.[146]

120. The original SGP, dated 6 June 2019, raised novelty as a ground of opposition and raised D3 as a relevant prior art publication. Currie-1 (as part of the EIS), also provided comments in relation to D3,[147] as well as the '256 application.[148] In my view, while the SGP may never had explicitly mentioned the opponent's reliance on the "whole of contents" provisions, the applicant would have known from the relevant priority and publication dates of D3 that if this document was being used for novelty purposes it would be being used under the "whole of contents" provisions. Furthermore, the evidence of Professor Currie in the EIS, directly addressed the disclosure of the '256 application. Why else would an expert witness lead evidence on a priority document of D3 if D3 was not intended to be raised as a "whole of contents" novelty document? As a result, I consider that the applicant was not unfairly prejudiced as they had an opportunity to lead evidence on the applicability of D3 as a novelty citation. Furthermore, the applicant's argument that Professor Currie provides no evidence of whether or not the claims of D3 are entitled to claim priority from the '256 application, is an argument in relation to the veracity of the opponent's whole of contents novelty case, rather than whether the applicant is prejudiced by making that case.

121. On the day prior to the hearing the opponent provided two new documents related to the hearing. The first was a table comparing the opposed application with a corresponding US application discussed in the Whitehead declaration (**the comparison table**), and the second was a chronology of publications relating to the opposition (**the chronology**). At the hearing, while the applicant took no issue with the chronology, the applicant strongly objected to the comparison table being included in the evidence, as this table was advanced without any notice or evidentiary support. The opponent submits that the purpose of the comparison table was as an "aide memoir" to summarise a lot of information in the briefest possible fashion.

122. The comparison table comprises six columns. The two columns on the far left-hand side reference relevant paragraphs in the '256 application and D3 respectively, and the third column on the left-hand side recites the claims of the current opposed application. The two columns on the far right-hand side reference relevant paragraphs in US20140068797 and US61/652,086 respectively, and the third column on the right-hand side recites the claims of US15/188,924. As the '256 application and D3 are already in evidence, and referred to by Professor Currie in his declaration in EIS, I consider the two far left-hand columns merely duplicate material already in evidence. However, I consider that the claims of US15/188,924 and the paragraphs referred to in US20140068797 and US61/652,086 to not be in evidence as Professor Currie did not refer to these documents in his EIS. As a result, I will not consider these parts of the comparison table in my consideration of this opposition. For completeness, I note that I consider the contents of the chronology to already be in evidence.

123. The opponent submits that D3 discloses a method for altering a chromosomal sequence of a eukaryotic cell, comprising a) introducing into the eukaryotic cell (i) a Cas9 protein comprising an NLS to transport the Cas9 into the nucleus, (ii) a DNA targeting RNA

[146] Applicant's Written Submissions at [121].
[147] Currie-1 at [70]-[74].
[148] Currie-1 at [76]-[84].

comprising a first segment comprising a nucleotide sequence that is complementary to a sequence in the chromosomal DNA and a second segment that interacts with Cas9, and b) maintaining the cell under conditions permissive for cleavage of the chromosomal DNA to form a double stranded break.[149] The opponent further submits that the target DNA comprises a PAM sequence and that the nuclease activity cleaves target DNA to produce double-stranded breaks, which are repaired by the cell in one of two ways, (i) non-homologous end joining (NHEJ), and (ii) homology directed repair (HDR), with a donor sequence with homology with the cleaved target sequence.[150]

124. The applicant submits that D3 does not provide an enabling disclosure at the priority date.[151] However, the applicant in its submissions, relies on the evidence of Professor Cannon who only discusses the disclosure of the two relevant priority documents of D3 (US61/652,086 and the '256 application), and not the disclosure of D3 as filed.[152]

125. D3 discloses a method of promoting site-specific cleavage and modification of a target DNA in a cell, the method comprising introducing into the cell: (i) a DNA-targeting RNA, wherein the DNA-targeting RNA comprises (a) a first segment comprising a nucleotide sequence that is complementary to a sequence in the target DNA, and (b) a second segment that interacts with a site-directed modifying polypeptide, and (ii) a site directed modifying polypeptide comprising (a) an RNA-binding portion that interacts with the DNA-targeting RNA, and (b) an activity portion that exhibits nuclease activity that creates a double stranded break in the target DNA, wherein the site of the double strand break is determined by the DNA-targeting RNA, the contacting occurs under conditions that are permissive for nonhomologous end joining or homology directed repair, and the target DNA is cleaved and rejoined to produce a modified DNA sequence.[153] In addition D3 discloses the target DNA comprising a PAM sequence,[154] the DNA modifying peptide being a Cas9,[155] and the target cell being a eukaryotic cell including human cells, invertebrate cells, plant cells, a single cell eukaryote, insect cells and yeast cells.[156] D3 also discloses the use of the method to integrate donor DNA into the target DNA,[157] and discloses that the method can be ex vivo or in vitro.[158] Furthermore D3 discloses a fusion of a Cas9 polypeptide with a heterologous sequence that provides for subcellular localisation (eg. a NLS).[159] As a result, I consider D3 relevant to the novelty of claims 1 and 2.

126. In addition, D3 discloses that the NLS is located at the C-terminus of the endonuclease.[160] D3 also discloses that polynucleotide encoding the site directed modifying polypeptide is a single-, double- or multi-stranded DNA or RNA,[161] the polynucleotide may be chemically

[149] Applicant's Written Submissions at [65].
[150] Applicant's Written Submissions at [66].
[151] Applicant's Written Submissions at [131].
[152] Cannon at [112]-[222].
[153] D3 at [0024].
[154] D3 at [00256] and Claim 66.
[155] D3 at [0008], [0009], [0017], [0018], [0019], [0021], [0025], [0026] and Claim 73.
[156] D3 at [0017], [0018], [0021], [0024], [0025], [0026] [00139], [00274], [00464] and Claim 70.
[157] D3 at [00150] and [00296].
[158] D3 at [00274], [00304], [00313] and [00464].
[159] D3 at [00242], [00265], [00357] and [00563].
[160] D3 at [00570].
[161] D3 at [0090].

synthesised,[162] and the exogenous nucleic acid may be part of an expression vector.[163] Therefore, I consider D3 relevant to the novelty of claims 4-18.

127. The applicant further identifies a number of difficulties with the opponent's submission that the USPTO Office Action provides a proper evidentiary basis for the Delegate to find that the claims of D3 are entitled to a priority date of 19 October 2012.[164] Firstly, by correspondence dated 24 April 2020, the Commissioner excluded the Whitehead declaration.[165] Secondly, the opponent has adduced no evidence from any of skill in the art concerning the disclosure of US61/652,086, let alone whether that disclosure would enable the skilled reader to perform the invention of D3.[166] Finally, the observations of a US Patent Examiner during the course of prosecution is not a proper evidentiary basis to determine whether the whole of contents provisions of the *Patents Act* have been made out.[167]

128. I agree with the Delegate's Direction dated 25 May 2020, for the same reasons given in that direction, that the Whitehead declaration dated 11 February 2020 and accompanying annexures PW-1 to PW-3 are not properly in reply to the evidence in answer. At the hearing the opponent requested that, if I found that the Whitehead declaration was not properly in reply to the evidence in answer, the declaration be included in the evidence under regulation 5.23.

129. In *Merial Limited v Bayer Intellectual Property GmbH* [2015] APO 16, the Delegate concluded at [24] that "a decision under regulation 5.23 must have regard to the nature of the information, and whether the information is likely, if not certain, to change the outcome of the opposition in a significant way." At the hearing, the applicant submitted that the Whitehead declaration was not relevant, noting the comments of Beach J in *Meat & Livestock Australia Limited v Cargill Inc (No 2)* [2019] FCA 33 at [413], who stated, when considering the relevance of overseas prosecution to the exercise of the discretion conferred by s 105(1A) of the *Patents Act* "the prosecution of patent applications is jurisdiction specific given the different laws and procedures that apply". The opponent argued at the hearing that the Whitehead declaration could not be provided as EIS as, at that time, the applicant did not know that Professor Cannon would be giving evidence. I do not consider that the Whitehead declaration would be likely, if not certain, to change the outcome of the opposition in a significant way, as the observations of a US Patent Examiner, and even the comments of the same declarant in relation to a related application in the US, are not considered of high enough probative value to satisfy this requirement as that case was decided on different facts and under different laws. Therefore, the Whitehead declaration will not form part of the evidence in determining the opposition. As a result, the opponent has only led evidence in relation to the '256 application, therefore this is **the only priority document** I will consider relating to the right of D3 to priority.

[162] D3 at [0090].
[163] D3 at [00139].
[164] Applicant's Written Submissions at [122].
[165] Applicant's Written Submissions at [124].
[166] Applicant's Written Submissions at [125].
[167] Applicant's Written Submissions at [128].

'256 application

130. The '256 application discloses a method of site-specific modification of a target DNA, the method comprising contacting the target DNA with: (i) a DNA-targeting RNA, wherein the DNA-targeting RNA comprises (a) a first segment comprising a nucleotide sequence that is complementary to a sequence in the target DNA, and (b) a second segment that interacts with a site-directed modifying polypeptide, and (ii) a site directed modifying polypeptide comprising (a) an RNA-binding portion that interacts with the DNA-targeting RNA, and (b) an activity portion that exhibits site-directed enzymatic activity.[168] In addition, the '256 application discloses the target DNA comprising a PAM sequence,[169] the site directed modifying polypeptide comprising Cas9,[170] and the target cells being eukaryotic cells[171] including single cell eukaryotic organisms, plant cells, algal cells, fungal cells, invertebrate cells, mammalian cells and human cells.[172] The '256 application further discloses contacting the target DNA with a donor polynucleotide, wherein the donor polynucleotide or copies of the donor polynucleotide integrate into the target DNA.[173]

131. While the '256 application fails to disclose the fusion of a Cas9 polypeptide with a NLS to provide for subcellular localisation, the '256 application does disclose Protein Transduction Domains (PTDs)(also known as cell penetrating peptides) which may refer to a polypeptide, polynucleotide, carbohydrate, or organic or inorganic compound that facilitates traversing a lipid bilayer, micelle, cell membrane, organelle membrane, or vesicle membrane.[174] The '256 application discloses the PTD attached to another molecule to facilitate the molecule traversing a membrane, for example going from extracellular space to intracellular space, or cytosol to within an organelle.[175] Furthermore, the '256 application discloses a chimeric site-directed modifying polypeptide as a fusion polypeptide comprising a heterologous polypeptide and the RNA-binding portion of a naturally occurring or a modified site-directed modifying polypeptide.[176]

132. The opponent submits that although the term NLS is not explicitly used in the '256 application, the disclosure of PTDs in the '256 application, discloses and enables the use of a NLS in the claims of D3, as [00152] of the '256 application discloses that a PTD facilitates traversing a molecule from the cytosol to within an organelle. This submission was supported by Professor Currie who provides that it was well known by 6 December 2012 that a PTD could transport proteins into the nucleus of eukaryotic cells (i.e. perform a similar function to a NLS).[177] An alternate argument put forward by the opponent was that the reference to a "heterologous polypeptide" as a fusion with a RNA-binding portion of a site-directed modifying polypeptide as disclosed in the '256 application, provides an enabling disclosure of a Cas9 having an NLS, as a NLS is encompassed by the term

[168] '256 at Claim 60.
[169] '256 at [0019], Figures 16A-C, [0033], Figures 30A-C, [0080], [00194], [00329]-[00333], [00335], [00336], [00350]-[00352], [00355], [00357], [00358] and Claim 62.
[170] '256 at [0003], [0080], [00108], [00129], [00133] and Figure 2.
[171] '256 at [0083], [00163], [00203] and [00257].
[172] '256 at [00203], [00255] and Claim 36.
[173] '256 at Claim 75.
[174] '256 at [00152].
[175] '256 at [00152].
[176] '256 at [00179].
[177] Opponent's Written Submissions at [68](iii); Currie-2 at [87]-[89].

"heterologous polypeptide", and NLSs were well known in the art to work with other gene editing systems such as ZFNs and TALENs.[178]

133. The applicant submits that the '256 application does not entitle D3 to a priority date of 19 October 2012. Professor Cannon's evidence provides that the '256 application fails to enable a skilled person to make and use such a system for in vivo genome editing in eukaryotic cells.[179] Firstly, Professor Cannon submits that the experiments performed in the '256 application are performed in vitro, using recombinant Cas9 and in vitro synthesised guide RNAs using highly artificial DNA targets, in cell- and nucleus-free conditions, using purified components which do not reflect the complexities of a eukaryotic genome.[180] Secondly, Professor Cannon's evidence also suggested Professor Currie's evidence erred equating PTDs with NLSs, submitting that the '256 application describes a PTD as a "polypeptide permeant domain to promote uptake by the cell" which is not the same thing as a NLS.[181]

134. Professor Cannon cites a Nature Methods article[182] which described attempts to develop variants of ZFNs containing an added PTD. In this study, a PTD from HIV-1 Tat (an exemplary PTD disclosed in the '256 application) was used, *in addition to a NLS*, to provide the different function of cell penetration. Furthermore, Professor Cannon notes that it was not until US61/757,640 filed on 28 January 2013 (the third of D3's four priority documents) that a NLS was specifically described as a modification for Cas9[183] and importantly, the NLS sequences are not included as a subset of PTDs but rather, are described in separate paragraphs.[184] Furthermore, Professor Cannon notes that in the '256 application and US61/757,640, the word 'nucleus' or 'nuclear localization' are not used in relation to PTDs, rather PTDs are described as directing entry into a cell.[185]

135. I consider that on the balance of probabilities, the disclosure in the '256 application does not provide a clear enough and complete enough disclosure of the embodiment defined in D3 relating to site specific modification of a target DNA in a *eukaryotic cell*. The '256 application provides no examples of site-specific modification of a target DNA in a eukaryotic cell, and I consider it would be an undue burden on the person skilled in the art to adapt the highly reductionist *in vitro* DNA modification experiments disclosed in the '256 application to targeted *in vivo* modification in a eukaryotic cell. Moreover, in agreement with the evidence of Professor Cannon, I do not consider that the disclosure of a PTD provided in the '256 application provides an enabling disclosure for the use of a NLS in D3.

136. As a result, D3 is not considered part of the prior art base as in my view, D3 is not entitled to gain priority from the '256 application.

[178] Opponent's Written Submissions at [68](iv).
[179] Cannon at [124] and [125].
[180] Cannon at [113] and [114].
[181] Cannon at [152]-[161].
[182] Gaj et al., Nature Methods, Vol. 9, pages 805-807: Published online on 1 July 2012 (Cannon EXHIBIT 52).
[183] US61/757,640 at [002221], [00243], [00409], [00411], [00416]-[00419] and [00421].
[184] US61/757,640 at [00192].
[185] Cannon at [159].

Inventive Step

137. The test for whether an invention is obvious is to ask whether it would have been a matter of routine to proceed to the claimed invention. In *Wellcome Foundation Ltd v V. R. Laboratories (Aust.) Pty Ltd*[186] Aickin J stated:

> "The test is whether the hypothetical addressee faced with the same problem would have taken as a matter of routine whatever steps might have led from the prior art to the invention, whether they are the steps of the inventor or not."

138. More recently, the High Court in *Aktiebolaget Hassle v Alphapharm Pty Ltd* (***Alphapharm***)[187] referred with approval to this approach and further held:

> "That way of approaching the matter has an affinity with the reformulation of the 'Cripps question' by Graham J in *Olin Mathieson Chemical Corporation v Biorex Laboratories Ltd* [1970] RPC 157. This court had been referred to *Olin* in the argument in *Wellcome Foundation*. Graham J had posed the question:
>
>> 'Would the notional research group at the relevant date in all the circumstances directly be led as a matter of course to try [the claimed invention] in the expectation that it might well produce [the desired result]?'
>
> That approach should be accepted."

Expectation of success

139. The expectation of success was considered in *Nichia Corporation v Arrow Electronics Australia Pty Ltd* [2019] FCAFC2 (***Nichia***). The Full Court in *Nichia* indicated that "care is needed in evaluating the character of the expectation separately from the steps the skilled addressee would have taken", citing with approval the observation in *Generic Health Pty Ltd v Bayer Pharma Aktiengesellschaft*[188] at [71] that it "is difficult to think of a case where an expectation that an experiment might well succeed is not implicit in the characterisation of steps as routine and to be tried as a matter of course".[189] The Court in *Nichia* also observed that "the relevant test is not knowing that steps will or would or even may well work, but merely expecting that the steps may well work."[190]

140. The expectation of success was also considered in *Mylan Health Pty Ltd v Sun Pharma ANZ Pty Ltd* [2020] FCAFC 116 (***Mylan***) where the Full Court noted the primary judge's observation that "the reformulated Cripps question could receive an affirmative answer even if the person skilled in the art assessed the prospects of success at less than 'fifty-fifty'".[191] The Full Court in *Mylan* was "not persuaded that, when answering the question he had posed, the primary judge erred in concluding that a percentage-based analysis was not useful, especially when expressed in terms of 'no better than fifty fifty'".[192]

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[186] [1981] HCA 12 at [45]; 148 CLR 262 at 286.
[187] [2002] HCA 59; 56 IPR 129 at 142-143.
[188] [2014] FCAFC 73; (2014) FCR 336.
[189] *Nichia Corporation v Arrow Electronics Australia Pty Ltd* [2019] FCAFC 2 at [88].
[190] *Nichia Corporation v Arrow Electronics Australia Pty Ltd* [2019] FCAFC 2 at [89] and [99].
[191] *Mylan Health Pty Ltd v Sun Pharma ANZ Pty Ltd* [2020] FCAFC 116 at [122].
[192] *Mylan Health Pty Ltd v Sun Pharma ANZ Pty Ltd* [2020] FCAFC 116 at [148].

141. The High Court in *Alphapharm* strongly endorsed the United States Court's rejection of the "obvious to try" notion, quoting with approval Judge Rich in *In Re O'Farrell*:

> "[F]or many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious."[193]

142. The High Court then noted:

> "In In re O'Farrell, Judge Rich also said:
>
> > "The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. … In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."
>
> The reasoning in these and other United States authorities should be accepted in preference to the path apparently taken in the English decisions, particularly after the 1977 UK Act, upon which Alphapharm relied. The United States decisions reflect an approach to the subject closer to that adopted in *Minnesota Mining* and *Wellcome Foundation*."[194]

Common general knowledge

143. Common general knowledge (CGK) is the background knowledge and experience available to all those working in the relevant art:

> "The notion of common general knowledge itself involves the use of that which is known or used by those in the relevant trade. It forms the background knowledge and experience which is available to all in the trade in considering the making of new products, or the making of improvements in old, and it must be treated as being used by an individual as a general body of knowledge."[195]

144. It is not enough that information is recorded in a document, even one that is widely circulated. It is only part of the common general knowledge when it is generally known and accepted:

> "information does not constitute common general knowledge merely because it might be found, for example, in a journal, even if widely read by persons in the art … Reference in this regard is made to the words of Luxmoore J in *British Acoustic Films* (1936) 53 RPC

[193] *In Re O'Farrell* 853 F 2d 894 (1988) at 903.
[194] *Alphapharm* at [76].
[195] *Minnesota Mining & Manufacturing Co v Beiersdorf (Australia) Ltd* [1980] HCA 9; 144 CLR 253 at 292.

221 at 250, cited by Lehane J in *Aktiebolaget Hässle v Alphapharm Pty Ltd* (1999) 44 IPR 593; [1999] FCA 628 at 605 [39]:

> *In my judgment it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates. A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated. Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words, when it becomes part of their common stock of knowledge relating to the art.*"[196]

145. Justice Beach noted the difficulty in establishing recently disclosed information as common general knowledge in *Meat & Livestock Australia Limited v Cargill* [2018] FCA 51:

> "Now in my view it has not been established that the information in Venter had become part of the common general knowledge as at the priority date, although I accept that shotgun sequencing was well known. Venter was published before the priority date and the news that the human genome had been sequenced no doubt attracted some attention. But the relevant question is the nature of the information, if any, which had become generally accepted in the filed of bovine genetics and had become relevantly common general knowledge in the context that I am considering."

Inventive step in light of the common general knowledge

146. The opponent submits that the components of the CRISPR-Cas9 system were well known because of the widely acclaimed Jinek paper which it argues formed part of the common general knowledge by the priority date.[197] Professor Currie's evidence provides that the information described in the Jinek paper became well known very quickly to researchers interested in genome editing soon after it was published.[198] The applicant submits that the Jinek paper was published only shortly before the priority date, and even if it attracted significant interest in the scientific community, or even the broader public, there is no evidence to support the proposition that CRISPR Cas9 as a programmable gene editing technology had become so generally known that it formed part of the CGK.[199]

147. In my view, even if the information in the Jinek paper was well known very quickly to researchers in the field of genome editing, being "well known" falls short of being accepted without question by the bulk of those engaged in the genome editing field. The Jinek paper was published under four months before the priority date of the opposed application, and I consider the evidence is insufficient to establish that this paper forms part of the CGK. As a result, claims 1-18 are considered inventive in light of the common general knowledge.

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[196] *Ranbaxy v AstraZeneca* [2013] FCA 368; (2013) 101 IPR 11 at 51 [217].
[197] Opponent's Written Submissions at [115].
[198] Currie-1 at [44].
[199] Applicant's Written Submissions at [178]-[180].

Inventive step in light of the prior art

Jinek et al (2012)

148. Jinek, M. et al., Science, 2012, Vol. 337, pages 816-821 (designated **D1**) was published on 17 August 2012. Consequently it is part of the prior art base.

149. D1 is titled "a Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity". D1 discloses a CRISPR-associated (Cas) system where mature CRISPR RNA (crRNA) is base-paired to trans-activating crRNA (tracrRNA) and forms a two-RNA structure that directs the CRISPR-associated protein Cas9 to introduce double-stranded (ds) breaks in target DNA.[200] D1 also discloses that the dual-tracrRNA:crRNA, when engineered as a single RNA chimera (i.e. a guide RNA), also directs sequence-specific Cas9 dsDNA cleavage.[201] D1 further discloses that for the guide RNA-Cas9 to bind and cleave the target sequence, the target sequence needed to be associated with a PAM sequence.[202] Therefore D1 discloses all of the components of the programmable CRISPR-Cas9 genome editing system, including a guide RNA comprising a crRNA and a tracrRNA, a Cas9, a donor polynucleotide, and a PAM sequence adjacent to the target site. D1 fails to disclose the use of the CRISPR-Cas9 genome editing system in eukaryotic cells.

150. However, D1 does disclose a number of passages that discuss the potential of the methodology used in D1 to be used in genome editing:

> "Our study reveals a family of endonucleases that use dual-RNAs for site-specific DNA cleavage and highlights the potential to exploit the system for RNA-programmable genome editing"[203]
>
> …
>
> "Thereby raising the exciting possibility of developing a simple and versatile RNA directed system to generate dsDNA breaks for genome targeting and editing"[204]
>
> …
>
> "the possibility of a single RNA guided Cas9 is appealing due to its potential utility for programmed DNA cleavage and genome editing"[205]
>
> …
>
> "indicating that rational design of chimeric RNAs is robust and could, in principle enable targeting of any DNA sequence of interest with few constraints"[206]
>
> …

[200] D1 at Abstract.
[201] D1 at Abstract.
[202] D1 at Page 819, right hand column.
[203] D1 at Abstract.
[204] D1 at Page 816, middle column, last paragraph- right hand column, first paragraph.
[205] D1 at Page 820, left hand column, first paragraph.
[206] D1 at Page 820, middle column, first paragraph.

"We further show that the Cas9 endonuclease can be programmed with guide RNA engineered as a single transcript to target and cleave any dsDNA sequence of interest. The system is efficient, versatile, and programmable by changing the DNA target binding sequence in the guide chimeric RNA. Zinc finger nucleases and transcription activator like effector nucleases have attracted considerable interest as artificial enzymes engineered to manipulate genomes. We propose an alternative methodology based on RNA programmed Cas9 that could offer considerable potential for gene targeting and genome editing applications."[207]

151. The applicant submits that the statement "could offer considerable potential" in D1, reflects the speculative nature of the statement and that the statement conveys the lack of any specific knowledge by the authors as to whether CRISPR-Cas9 would actually work and be useful for genome editing in eukaryotic cells.[208] The applicant further submits that this cautious and qualified statement in D1 stands in stark contrast to Professor Currie's unfounded assertions that, by 6 December 2012, it was clear that CRISPR-Cas9 "could easily and successfully be applied to a range of eukaryotic cells."[209]

152. The opponent submits that the problem to be solved by the current application is "the need to produce an alternative targeted genome modification system not requiring the design of a new nuclease for each targeted genomic location.[210] This formulation of the problem does not appear to be in dispute.

153. At the hearing it did not appear to be in dispute that in light of the problem and in view of D1, the next steps for a person skilled in the art would be to design experiments to see if the CRISPR-Cas9 technology demonstrated in prokaryotes in D1, could be adapted to work in eukaryotes. For example, the opponent submitted that Professor Currie's evidence supports a finding that D1 would have led the person skilled in the art to do everything with CRISPR-Cas9 that had been done with ZFN and TALEN genome editing methodologies, including introducing exogenous DNA into eukaryotic cells or organisms.[211] What is in dispute however, is whether there would be the requisite expectation that such experiments would be successful?

154. The opponent submits that there would be the requisite expectation of success for two main reasons. Firstly, there would be the requisite success based on the success of other well-known gene editing systems in eukaryotic cells. Secondly, there is objective evidence of experiments conducted post D1 that would have established this reasonable expectation of success at the priority date. I will now address each of these arguments in turn.

<u>Expectation of success based on other well-known gene editing systems in eukaryotic cells</u>

155. Professor Currie's evidence states that he expected the prokaryotic experiments disclosed in D1 to work in a eukaryotic environment based on the success of other well-known gene editing systems that worked in eukaryotic cells.[212] Professor Currie drew analogies with

[207] D1 at Page 820, middle column, second paragraph – right hand column, last paragraph.
[208] Applicant's Written Submissions at [211]; Cannon at [70].
[209] Applicant's Written Submissions at [212]; Cannon at [70].
[210] Opponent's Written Submissions at [107].
[211] Opponent's Written Submissions at [119]; Currie-1 at [55] and [56].
[212] Currie-1 at [63].

other methodologies reliant on targeting bacterial endonucleases, such as ZFN and TALEN, which successfully functioned in a range of eukaryotic genomic DNA manipulations, including triggering HDR and NHEJ.[213] Professor Currie further stated that the inclusion of a NLS could be used to transport the CRISPR-Cas9 components into the nucleus of a eukaryotic cell, and this was "ancient" technology at the earliest priority date of the opposed application.[214]

156. The applicant responded to this evidence by arguing that at the priority date, it was known that CRISPR-Cas systems are unique to prokaryotic cells and there is no equivalent system in eukaryotic cells.[215] The applicant submits that adapting the CRISRP-Cas9 methodology used in D1 to use in eukaryotic cells necessitates a different approach, raising numerous "uncertainties" as to whether such experiments would be expected to work. Firstly, D1 fails to provide any evidence that the CRISPR-Cas9 system can be harnessed to introduce double stranded DNA cleavage in eukaryotic cells, much less in a manner that might be compatible with genome editing.[216] Secondly, the use of a reconstituted *in vitro* system in D1, with minimal extraneous (non-target) DNA sequences to provide potential competition does not therefore confer the requisite expectation that CRISPR-Cas9 would work to find and modify a specific target sequence in the enormously complex world of a eukaryotic nucleus,[217] including the presence of histones and a nuclear membrane.[218] Finally, the applicant submits that the fact that NLS has been used in different applications provides no basis to assert a reasonable expectation that a NLS could be placed appropriately on an entirely different protein, Cas9, which operates in an entirely different manner.[219]

157. In response to the applicant's argument regarding adapting prokaryotic genome editing systems to eukaryotes, Professor Currie submits that many bacterial/bacteriophage proteins had been successfully expressed in functional forms in eukaryotic cells such as the Cre recombinase of the Cre-LoxP genome editing system,[220] phiC31 integrases,[221] the tetracycline repressor protein,[222] and the lac repressor protein of the Lac operator/repressor system.[223] The applicant rejects this proposition, arguing that these limited examples were selected in hindsight, and that just because some non-eukaryotic proteins have been used in entirely unrelated methods in eukaryotic cells, does not provide an assumption that the CRISPR-Cas9 system would work in eukaryotic cells.[224]

158. Professor Cannon rejects this evidence of Professor Currie for two main reasons. Firstly, Professor Cannon considers it a considerable oversimplification to conclude that just because ZFNs and TALENs functioned successfully in eukaryotic cells, that CRISPR-Cas9 systems would as well, as targeted genetic engineering is not a generic method and each of the designed nuclease types (such as meganucleases, zinc finger nucleases, TAL effector nucleases, and RNA-guided nucleases such as Cas9) interacts with its target DNA using a

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[213] Currie-1 at [63].
[214] Currie-1 at [27], [28] and [62]; Currie-2 at [71].
[215] Applicant's Written Submissions at [186].
[216] Applicant's Written Submissions at [187].
[217] Applicant's Written Submissions at [192].
[218] Applicant's Written Submissions at [194].
[219] Applicant's Written Submissions at [197].
[220] Currie-2 at [35].
[221] Currie-2 at [37].
[222] Currie-2 at [38].
[223] Currie-2 at [39].
[224] Applicant's Written Submissions at [201] and [202].

distinct set of molecular principles.[225] For example, zinc-finger nucleases and TAL effector nucleases bind along the major groove of B-form double-helical DNA, or to DNA that has experienced a modest degree of structural distortion as a consequence of being assembled into chromatin,[226] whereas nucleases from bacterial CRISPR systems, such as Cas9, do not bind in their catalytically active state, to regular, or even modestly distorted, B-form DNA.[227]

159. Professor Cannon goes on to state:

> "Instead, Cas9, guided to its target by an RNA, unwinds the DNA double helix, separates the strands, and forms a three-way molecular complex, in which the Cas9-bound RNA forms a Watson-Crick heteroduplex with one DNA strand in the context of an extended stretch of fully unwound genomic DNA."[228]
>
> …
>
> "Therefore, by 6 December 2012, for all known cases of successful genome engineering in eukaryotic cells, embryos or organisms using targeted nucleases, the specificity of DNA binding had been provided by wholly eukaryotic components. There were no precedents to suggest that the prokaryotic CRISPR-Cas9 system, which had no analog in eukaryotic cells, would function in such an environment and knowledgeable people by 6 December 2012 would be aware of this uncertainty."[229]

160. The applicant concludes by submitting whilst it may have been obvious to try to explore a new technology or general approach that seemed to be a promising field of experimentation, D1 gave only general guidance as to the particular form of the claimed invention or how to achieve it and therefore the requisite expectation of success has not been established.

Objective evidence of experiments post D1

161. The opponent submits that the objective evidence of what experiments actually *were* conducted post D1 suggests that there should have been a reasonable expectation of success by the person skilled in the art at the priority date that the D1 experiments would work in eukaryotes. For example, in January 2013, Professor Keith Joung reported he had a paper in press that applied the CRISPR methodology to Zebrafish, and to have a paper in press at that time meant he would have been conducting experiments well before the priority date of 6 December 2012.[230]

162. The applicant argues that while Professor Currie may have been excited by the *possibility* at the priority date that CRISPR-Cas9 might be adapted in the future to work in eukaryotic cells, the objective real-world evidence strongly suggests otherwise.[231] Firstly, despite Professor Currie's evidence that CRISPR-Cas9 was cheaper and easier to use than ZFNs

[225] Cannon at [96].
[226] Cannon at [97].
[227] Cannon at [98].
[228] Cannon at [98].
[229] Cannon at [99].
[230] Opponent's Written Submissions at [117]; Currie-1 at [48].
[231] Applicant's Written Submissions at [164] and [165].

and TALENS, Professor Currie continued to use TALENS and ZFNs for targeting genes in eukaryotic cells for at least a further four years after the priority date.[232] Secondly, the academic commentary around the time of the publication of D1 reflect the actual uncertainty as to whether CRISPR-Cas9 could ever work in eukaryotic cells.[233] One example was in Molecular Therapy, the Journal of the American Society of Gene and Cell Therapy, where Dr Dana Carroll states in her commentary:

> "What about activity of the system in eukaryotic cells? Both zinc fingers and TALE modules come from natural transcription factors that bind to their targets in a chromatin context. *This is not true of the CRISPR components. There is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA-RNA hybrid can be stabilized in that context* [emphasis added]. This structure may be a substrate for RNA hydrolysis by ribonuclease H and/or FEN1, both of which function in the removal of RNA primers during DNA replication. Only attempts to apply the system in eukaryotes will address these concerns."[234]

163. Another example was from the authors of D1, who in an article summarising the progress in the field up to and including the publication of D1 stated:

> "These findings suggest the exciting possibility that Cas9:sgRNA complexes might constitute a simple and versatile RNA-directed system for generating DSBs that could facilitate site-specific genome editing. *However, it was not known whether such a bacterial system would function in eukaryotic cells* [emphasis added]."[235]

164. A further example is a 2014 article profiling Dr. Doudna which states:

> "*Doudna experienced 'many frustrations' getting CRISPR to work in human cells* [emphasis added]. But she knew if she succeeded, CRISPR would be 'a profound discovery' – and maybe even a powerful gene therapy technique."
>
> "'I hope you're sitting down', an excited colleague told Doudna in an unexpected phone call. 'CRISPR is turning out to be absolutely spectacular in [Harvard geneticist] George Church's hands.' He had even gotten it to work in human cells. Thrilled, Doudna immediately contacted Church. They shared their results, and both published studies in January 2013 showing that CRISPR can cut, delete and replace genes in human cells."[236]

165. Finally, the applicant submits that when genome editing applications using CRISPR Cas9 in eukaryotic cells were actually demonstrated after the priority date, the unexpectedness of this finding was reflected in the fact that the papers were accepted for publication in high impact journals including *Science*.[237]

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[232] Applicant's Written Submissions at [166]; Currie-1 at [10].
[233] Applicant's Written Submissions at [168].
[234] Cannon at [72].
[235] Cannon at [74] and Exhibit 28 (RNA-programmed genome editing in human cells, eLIFE, 2013, Vol. 2, p. e00471).
[236] Cannon [76] and Exhibit 29.
[237] Applicant's Written Submissions at [173].

Consideration

166. The key area of disagreement between the experts is in relation to whether it could be reasonably expected that the prokaryote CRISPR-Cas9 system disclosed in D1 could be adapted to work for gene editing in eukaryotes. The question is whether the steps taken in adapting the prokaryotic CRISPR-Cas9 system disclosed in D1, to achieve targeted genomic modification of eukaryotic cells, would be taken as a matter of routine. As noted in *Nichia*, in most cases the expectation that an experiment might well succeed is implicit in the steps being characterised as routine and to be tried as a matter of course.

167. As discussed above, the evidence of Professor Cannon identifies a number of matters as engendering substantial uncertainty as to whether targeted genomic modification of eukaryotic cells using the CRISPR-Cas9 system was attainable. Most relevantly, as the prokaryotic CRISPR-Cas9 system has no analog in eukaryotic cells, there would be substantial uncertainty whether such a system would work in eukaryotic cells. Furthermore, I consider that the comparison with ZFNs and TALENs, does not assist in providing this level of certainty. Although CRISPR-Cas9, ZFNs and TALENs are all nuclease systems, they each interact with their target DNAs using different principles. Both zinc fingers and TALE modules come from natural transcription factors that bind to their targets in a chromatin context, whereas Cas9 nucleases do not. As a result of this uncertainty, I do not consider the steps to achieve targeted integration in eukaryotes would be a matter of routine, as it is not clear whether there was a reasonable expectation that such steps would work. Therefore, I consider that the pursuit of targeted genomic integration in eukaryotic cells by adapting the prokaryote system disclosed in D1 is more in the nature of a "worthwhile to try" research project, than a routine undertaking.

168. It follows that I cannot be satisfied on the balance of probabilities, that the person skilled in the art would have a reasonable expectation, rather than a hope, of successfully achieving targeted genomic integration in eukaryotic cells in light of the disclosure of D1. Therefore claims 1-18 are considered inventive in light of D1.

Jinek et al (2012) and Brouns 2012

169. Brounds, S. J. J., Science, 2012, Vol. 337, pages 808-809 (designated **D2**) was published on 17 August 2012. Consequently it is part of the prior art base.

170. D2 is a commentary on D1 and is published in the same journal. D2 discloses that D1 shows that cleavage was robust and occurred with multiple turnovers in both relaxed and supercoiled DNA targets.[238] D2 also discloses that D1 demonstrates that a highly specific, customisable RNA directed DNA nuclease could be useful to edit whole genomes, and that based on the 20 nucleotide guide section of the crRNA, the enzyme could theoretically introduce breaks at unique sites in any eukaryotic genome.[239] Furthermore, D2 discloses that introducing DNA breaks at desired loci using just Cas9 and a chimeric crRNA would be a substantial improvement over existing gene targeting technologies, such as zinc finger nucleases and transcription activator like effector nucleases, as these require protein engineering for every new target locus.[240]

[238] D2 at Page 809, left hand column, first full paragraph.
[239] D2 at Page 809, left hand column, first full paragraph.
[240] D2 at Page 809, middle column, second full paragraph.

171. The opponent submits that D2 provides further objective evidence that before the earliest priority date, the PSA would have understood D1 to be disclosing a system capable of use in eukaryotic genome editing and taken well-known and routine steps to apply that system to desired ends, and that D2 reinforces that the CRISPR-Cas9 methodology could be used for any cell type, to "edit whole genomes" and "introduce breaks at unique sites in any eukaryotic genome."[241] The applicant submits that the language in D2 that the method "could be useful" to "theoretically" introduce breaks at unique sites in any eukaryotic genome, does not suggest the expectation of success as contended by the opponent.[242]

172. In my view, D2 adds no further disclosure that would overcome the shortfalls of the opponent's case with regard to inventive step in light of D1. That is, I do not consider that the desired goal of trying the CRISPR-Cas9 system to successfully integrate donor DNA into a target eukaryotic DNA sequence, would (in light of D1 and D2) have the requisite expectation of success. Therefore, claims 1-18 are considered inventive in light of a combination of D1 and D2.

Support

173. Section 40(3) as amended by the *Raising the Bar Act* requires that the claims must be supported by matter disclosed in the specification. The requirement of support can be summarised as requiring that the scope of the claims "should correspond to the technical contribution to the art".[243]

174. The requirement of support has been more fully explained as follows:

> "in other words it is the definition of the invention in the claims that needs support. In the Board's judgement, this requirement reflects the general legal principle that the extent of the patent monopoly, as defined by the claims, should correspond to the **technical contribution to the art** in order for it to be supported, or justified. This means that the definitions in the claims should essentially correspond to the scope of the invention as disclosed in the description. In other words, as was stated in Decision T 26/81, the claims should not extend to subject-matter which, after reading the description, would still not be at the disposal of the person skilled in the art. Consequently, a technical feature which is described and highlighted in the description as being an essential feature of the invention, must also be a part of the independent claim or claims defining this invention."[244]
> (emphasis in the original, citations omitted)

175. To determine whether the requirements of support are satisfied the following steps were set out in *CSR Building Products Limited v United States Gypsum Company* (***CSR***):[245]

(i) construe the claims to determine the scope of the invention as claimed,
(ii) construe the description to determine the technical contribution to the art, and
(iii) decide whether the claims are supported by the technical contribution to the art.

[241] Opponent's Written Submissions at [129].
[242] Applicant's Written Submissions at [214].
[243] *Fuel Oils/EXXON* (T409/91) [1994] OJ EPO 653 at 659.
[244] *Fuel Oils/EXXON* (T409/91) [1994] OJ EPO 653 at 659 and 660.
[245] [2015] APO 72 at [115].

176. There is substantial overlap in the submissions of the opponent in relation to section 40(3) and section 40(2)(a), in relation to whether there is an enabling disclosure. I have already considered these submissions above and will not revisit them here.

177. The opponent submits that while the alleged technical contribution is "targeted genome modification", in particular methods of using RNA-guided endonucleases or fusion proteins comprising CRISPR/Cas-like proteins to modify or regulate targeted chromosomal sequences,[246] the true technical contribution is the idea of adding a NLS to Cas9 for use in eukaryotic genome modification.[247] The opponent further submits that none of the claims are limited to the steps taken in Experiment A i.e. limiting the claims to pre-annealed crRNA-tracrRNA and excluding chimeric RNA.[248] The applicant argues that the opponent mischaracterises the technical contribution to the art as the idea of adding a NLS to Cas9.[249] The applicant submits that the technical contribution to the art is establishing that Cas9 could be used for genomic manipulation in eukaryotic cells.[250]

178. As can be seen from *CSR*, the technical contribution is determined by construing the description of the opposed application. From a construction of the opposed application, I consider the technical contribution to be a method for modifying a chromosomal sequence in a eukaryotic cell, wherein the method comprises introducing into the eukaryotic cell: (i) a Cas9 comprising a NLS, (ii) a guide RNA, and (iii) a donor polynucleotide, such that the chromosomal sequence is modified by insertion or substitution of the donor sequence into the chromosomal sequence. As previously discussed under claim construction, I consider the scope of the claims to be commensurate with the applicant's technical contribution to the art, and therefore supported by that technical contribution to the art.

Best Method of Performance

179. Section 40(2)(aa) of the *Patents Act* requires that a complete specification must:

> "disclose the best method known to the applicant of performing the invention."

180. In *American Cyanamid Company v Ethicon Limited* [1979] RPC 215 at page 269, it was stated:

> "The Act is intending to protect the public against a patentee who deliberately keeps to himself something novel and not previously published which he knows of or has found out gives the best results, with a view to getting the benefit of a monopoly without giving to the public the corresponding consideration of knowledge of the best method of performing the invention."

181. In *Expo-Net Danmark A/S v Buono-Net Australia Pty Ltd (No 2)* (***Expo-Net***)[251] Bennett J stated:

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[246] Opponent's Written Submissions at [273].
[247] Opponent's Written Submissions at [274].
[248] Opponent's Written Submissions at [275].
[249] Applicant's Written Submissions at [249].
[250] Applicant's Written Submissions at [249].
[251] [2011] FCA 710.

> "it must be established that there was a better method known to the applicant at the date of filing the patent than the one described in the specification. This is clearly a subjective question." (*Expo-Net* at [15])
>
> and
>
> "To that end it is necessary first to understand what the invention is. Indeed, this is perhaps the first question that needs to be answered". (*Expo-Net* at [16])

182. The opponent submits that the applicant has not disclosed the best method of identifying successfully modified sequences.[252] The opponent cites the evidence of Dr Urnov which was referred to in Professor Cannon's evidence,[253] that the use of a PCR assay using Accuprime Taq polymerase (Invitrogen) avoids the problem of nonzero false negative rate in PCR amplification assays.[254] The opponent's argument is based on the fact that the applicant should have "knew or believed" that using the Accuprime method instead of the method used in Example 5 of the opposed application was a better method for confirming whether there was chromosomal integration in samples B-D.[255] The applicant submits that the opponent has adduced no evidence to support the various assertions it makes concerning Dr Urnov's evidence. That is, there is simply no credible evidence upon which it could be said that the applicant has withheld a better method known to it at the time of filing.[256]

183. As can be seen from *Expo-Net*, to fall foul of the best method of performance provisions in the *Patents Act*, the evidence must establish that "there was a better method *known* [emphasis added] to the applicant". The opposed specification details two methods of determining whether a donor polynucleotide was successfully integrated into the chromosome of a eukaryotic cell, a FACS method (Example 4) and a confirmatory PCR method (Example 5). I consider that while Dr Urnov's evidence at best, may identify that he knew of a different method of PCR assay to test for targeted integration (Accuprime Taq polymerase (Invitrogen)), this evidence falls well short of establishing that *the applicant knew* of a better method than the one they described in the opposed specification, and they were deliberately withholding it.

184. As a result, I consider that the applicant provided a best method of performing the invention.

Utility

185. Section 18(1)(c) of *the Patents Act* requires that for an invention to be patentable it must be useful. This requirement was expressed in the following manner at [141] of *Ranbaxy Australia Pty Ltd (CAN 110 781 826) v Warner-Lambert Company LLC* [2008] FCAFC 82:

> "Under ss 138 and 18(1)(c) of the 1990 *Act*, it is a ground of invalidity if the claimed invention is not useful "so far as claimed in any claim". If the claimed invention does what it is intended by the patentee to do and the end obtained is itself useful, the invention is

[252] Opponent's Written Submissions at [285].
[253] Cannon at [56]-[58]; Exhibit 27.
[254] Opponent's Written Submissions at [286].
[255] Opponent's Written Submissions at [287].
[256] Applicant's Written Submissions at [256].

useful within the meaning of s 18(1)(c) (see *Rehm Pty Limited v Webster's Security Systems (International) Pty Limited* (1981) 81 ALR 79 at 96; *Welcome Real-Time SA v Catuity Inc* [2001] FCA 445; (2001) 113 FCR 110 at 144; and *Fawcett v Homan* (1896) 13 RPC 398 at 405). As to the first aspect, the invention as claimed must attain the result promised by the patentee (*Advanced Building Systems Pty Limited v Ramset Fasteners (Aust) Pty Limited* [1998] HCA 19; (1998) 194 CLR 171 at 187)."

186. The principles of utility were summarised by the Full Court of the Federal Court in *Artcraft Urban Group Pty Ltd v Streetworx Pty Ltd* [2016] FCAFC 29 at [120]-[121] (with references omitted):

> "The 'basic principle' of inutility is that if an invention 'does what it is intended by the patentee to do, and the end attained is itself useful, the invention is a useful invention'. What the invention is 'intended' to do is a matter to be gathered from 'title and the whole of the specification'.
>
> Put another way, the two questions are: first, what is the promise of the invention derived from the whole of the specification?; second, by following the teaching of the specification, does the invention, as claimed in the patent, attain the result promised for it by the patentee? Further, 'everything' that is within the scope of a claim must be useful, that is, attain the result promised for the invention by the patentee."

187. The opponent makes two arguments on lack of utility. Firstly, each of the claims include within their scope methods that do not produce the desired or promised result, namely, modification of a chromosomal sequence in a eukaryotic cell by integrating a donor sequence at a target site.[257] Secondly, each of the claims include embodiments that will not work as a matter of principle.[258] In relation to the first argument, the applicant responds by submitting that it is apparent from the wording of the claims that they exclude from their scope methods that do not produce the desired or promised result, the modification of a chromosomal sequence in a eukaryotic cell by integrating a donor sequence at a target site.[259] In relation to the second argument, the applicant submits that the opponent's submission misunderstands the scope of the claims which are all limited to methods which actually integrate a donor sequence into a target site, and the claims therefore exclude guide RNAs, donor sequences, cleavage sites or Cas9 proteins which do not result in integration of the donor sequence.[260]

188. The parties agree that the promise of the invention is the modification of a chromosomal sequence in a eukaryotic cell by *integrating* a donor sequence. The next question is: Does the invention as claimed, attain the result promised for it by the patentee? As discussed previously under construction, I consider that the scope of the claims are limited to methods using only guide RNAs, Cas9s and donor polynucleotides that actually result in targeted *integration* of a donor sequence in the eukaryotic chromosome. I further considered that site specific integration has occurred in treatments A-D. It follows that the promise of the invention has been attained across the full scope of the claims. As a result, claims 1-18 are considered to be useful.

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[257] Opponent's Written Submissions at [248].
[258] Opponent's Written Submissions at [251].
[259] Applicant's Written Submissions at [235].
[260] Applicant's Written Submissions at [239] and [240].

Manner of Manufacture

189. Section 18(1)(a) of the Act requires that the invention, so far as claimed in any claim, must be a manner of manufacture within the meaning of section 6 of the Statute of Monopolies. The High Court in *National Research Development Corporation v Commissioner of Patents* (***NRDC***)[261] laid out the proper question for determination when considering manner of manufacture as:

> "Is this a proper subject according to the principles which have developed for the application of s. 6 of the Statute of Monopolies?"[262]

190. With this at the fore of their considerations in respect of a claim to a process for eradicating weed from a stretch of land, the High Court in *NRDC* described subject matter that would be considered patentable:

> "The point is that a process, to fall within the limits of patentability which the context of the Statute of Monopolies has supplied, must be one that offers some advantage which is material, in the sense that the process belongs to a useful art as distinct from a fine art ... that its value to the country is in the field of economic endeavour."[263]

191. Whether an invention is a manner of manufacture can also be assessed by asking whether the claimed invention lacks the necessary quality of inventiveness on the face of the specification.[264]

192. Another formulation of the requirement is found in *Commissioner of Patents v Microcell Ltd*[265]:

> "We have in truth nothing but a claim for the use of a known material in the manufacture of known articles for the purpose of which its known properties make that material suitable. A claim for nothing more than that cannot be subject matter of a patent."

193. The opponent submits the invention claimed in the opposed application was described in D1 which is referred to in paragraph [0022], and that the opposed application claims methods using the CRISPR-Cas9 system, a known programmable genome editing system, and well-known molecular biology techniques, such as the use of a NLS and transfection techniques to produce an expected result i.e. the claims relate to a known system with known properties for a known purpose in a known manner.[266]

194. The applicants submit that it cannot be said that the specification "on its face" lacks the necessary quality of inventiveness because the specification does not admit that the methods claimed were not new or inventive, nor does it support the drawing of any

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[261] [1959] HCA 67; 102 CLR 252.
[262] *NRDC* at [269].
[263] *NRDC* at [275].
[264] *NV Philips Gloeilampenfabrieken v Mirabella International Pty Ltd* [1995] HCA 15 at [9]; [1995] HCA 15; (1995) 183 CLR 655 at 663-665.
[265] (1959) 102 CLR 232 at 251.
[266] Opponent's Written Submissions at [170] and [173].

inference to that effect.[267] In fact, the opposed specification positively asserts that the claimed method is a significant advance over the prior art.[268]

195. I find the applicant's submission persuasive. While D1 is referenced in the opposed application, I have found previously that the claims are considered inventive in light of D1. It follows therefore, that the claimed invention does not lack the necessary quality of inventiveness on the face of the specification. As a result, claims 1-18 are considered to be for a manner of manufacture.

Conclusion

196. The opposition fails on all grounds.

Costs

197. It is normal in matters before the Commissioner that costs should follow the event. I see no reason to depart from that approach in the present case. I will award costs according to Schedule 8 against the opponent.

Damian Triffett
Delegate of the Commissioner of Patents

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[267] Applicant's Written Submissions at [225].
[268] Applicant's Written Submissions at [225].

ANNEX

1. A method for modifying a chromosomal sequence in a eukaryotic cell by integrating a donor sequence, the method comprising:
   a) introducing into the eukaryotic cell
   (i) at least one RNA-guided endonuclease comprising at least one nuclear localization signal or nucleic acid encoding at least one RNA-guided endonuclease comprising at least one nuclear localization signal, wherein the at least one RNA-guided endonuclease is a clustered regularly interspersed short palindromic repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR/Cas) type II system protein and the CRISPR/Cas type II system protein is a Cas9 protein,
   (ii) at least one guide RNA or DNA encoding at least one guide RNA, and
   (iii) a donor polynucleotide comprising the donor sequence; and
   b) culturing the eukaryotic cell such that each guide RNA guides an RNA-guided endonuclease to a target site in the chromosomal sequence, the RNA-guided endonuclease introduces a double-stranded break at the target site, and the double-stranded break is repaired by a DNA repair process such that the chromosomal sequence is modified by insertion or substitution of the donor sequence into the chromosomal sequence, wherein
   the target site in the chromosomal sequence is immediately followed by a protospacer adjacent motif (PAM),
   the method does not comprise a process for modifying the germ line genetic identity of a human being and, wherein
   the method does not comprise a method for treatment of the human or animal body by surgery or therapy.

2. An ex vivo or in vitro method for modifying a chromosomal sequence in a eukaryotic cell by integrating a donor sequence, the method comprising:
   a) introducing into the eukaryotic cell
   (i) at least one RNA-guided endonuclease comprising at least one nuclear localization signal or nucleic acid encoding at least one RNA-guided endonuclease comprising at least one nuclear localization signal, wherein the at least one RNA-guided endonuclease is a clustered regularly interspersed short palindromic repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR/Cas) type II system protein and the CRISPR/Cas type II system protein is a Cas9 protein,
   (ii) at least one guide RNA or DNA encoding at least one guide RNA, and
   (iii) a donor polynucleotide comprising the donor sequence; and
   b) culturing the eukaryotic cell such that each guide RNA guides an RNA-guided endonuclease to a target site in the chromosomal sequence, the RNA-guided endonuclease introduces a double-stranded break at the target site, and the double-stranded break is repaired by a DNA repair process such that the chromosomal sequence is modified by insertion or substitution of the donor sequence into the chromosomal sequence, wherein
   the target site in the chromosomal sequence is immediately followed by a protospacer adjacent motif (PAM) and, wherein
   the method does not comprise a process for modifying the germ line genetic identity of a human being.

3. The method of any previous claim, wherein the target site is a Rosa26 locus, a HPRT locus, or an AAVS1 locus.

4. The method of any previous claim, wherein the at least one nuclear localization signal is located at the C-terminus of the endonuclease.

5. The method of any previous claim, wherein each guide RNA comprises a first region that is complementary to the target site in the chromosomal sequence.

6. The method of any previous claim, wherein each guide RNA comprises a second region that interacts with the RNA-guided endonuclease.

7. The method of any previous claim, wherein the donor sequence in the donor polynucleotide has at least one nucleotide change relative to the chromosomal sequence near the target site in the chromosomal sequence.

8. The method of any previous claim, wherein the donor sequence in the donor polynucleotide is flanked by sequences having substantial sequence identity to sequences located upstream and downstream of the target site in the chromosomal sequence.

9. The method of any previous claim, wherein the donor polynucleotide further comprises a targeted cleavage site that is recognized by the RNA-guided endonuclease.

10. The method of any previous claim, wherein the nucleic acid encoding the RNA-guided endonuclease is mRNA.

11. The method of any of claims 1-9, wherein the nucleic acid encoding the RNA-guided endonuclease is DNA.

12. The method of claim 11, wherein the DNA is part of a vector that further comprises sequence encoding the guide RNA.

13. The method of any of claims 1-12, wherein the eukaryotic cell is a human cell, a non-human mammalian cell, or a non-human mammalian embryo.

14. The method of any of claims 1-12, wherein the eukaryotic cell is an invertebrate cell, an insect cell, a plant cell, a yeast cell or a single cell eukaryotic organism.

15. The method of claim 14, wherein the eukaryotic cell is a plant cell.

16. The method of any of claims 1-15, wherein the eukaryotic cell is *in vitro*.

17. The method of claim 1, wherein the eukaryotic cell is *in vivo*.

18. The method of any previous claim, wherein the at least one guide RNA is chemically synthesized.