ASX/Media Release

Benitec US Reexam Update

12 March 2008, Melbourne, Australia: The Directors of Benitec Limited (ASX:BLT) provide the following with regard to the updated Graham declaration filed to the USPTO for Reexamination of U.S. Patent No. 6,573,099 - GENETIC CONSTRUCTS FOR DELAYING OR REPRESSING THE EXPRESSION OF A TARGET GENE ("the '099 Patent").

The communication lodged this week brings to the Examiner's attention an error that exists in the Declaration under 37 C.F.R. §1.131 of Michael Graham dated 24 April 2007, submitted in this merged reexamination proceeding. Paragraph 9 of that Declaration contains a description/exhibit that is incorrect regarding an aspect of certain embodiments of the invention, i.e., the stuffer fragment. Accordingly, a new Declaration by Dr. Graham has been provided.

This new Declaration shows conception of that aspect of the invention before the critical date, 23 December 1997. We believe that the error arose in preparing the first Declaration submitted in the Reexamination, filed 28 November 2005. A copy of the new Declaration is included with this release. Due to the file size, it may be more convenient to obtain a full copy of the filing on USPTO PAIRS.

Benitec has rights to all human therapeutic applications for the '099 Patent and the other related patents in the gene silencing family in the US. These include patent application nos. 10/346,853, 10/759,841, 10/821,726, 09/646,807, 10/646,070, and 10/821,710. Benitec is confident that the gene silencing claims will be further secured through the reexamination of the '099 patent and these related patents or patent applications.

Background on the US Reexamination

Nucleonics initiated a third party Reexamination at the U.S. Patent and Trademark Office ("USPTO") on 4 October 2004, providing the USPTO with art it asserted invalidated the '099 Patent. The USPTO rejected the claims based on the provided art. Benitec successfully overcame the references, and the USPTO withdrew all rejections but instituted new rejections on additional art it had uncovered. Benitec then filed a response, which it believed overcame the rejections of Record.

Nucleonics then requested a second Reexamination, adding art it asserted invalidated the '099 Patent. The USPTO merged the two Reexaminations and sent out an Office Action. The USPTO withdrew most of the earlier rejections it made, modified other rejections, and added rejections based on the art Nucleonics provided in its second Reexamination request.

In January 2007, the USPTO issued a non final rejection. Benitec reviewed the new material and believed it did not raise any issues that would preclude patentability of the invention disclosed in the '099 Patent. Benitec also believed it has strong arguments for overcoming the art of record. Benitec responded to the rejections found in the merged Reexaminations on 24 April 2007 after a 1 month extension was granted. Benitec believed that its April 24th submission fully responded to all of the issues raised by the Patent Office and persuasively explained why the prior art did not anticipate or render obvious the claims under Reexamination.

On 3 August 2007, Benitec submitted a summary of an Examiner Interview its patent attorneys conducted with the U.S. Patent and Trademark Examiners responsible for the Reexamination of the '099 Patent. A supplemental amendment was also filed for procedural matters and to update the Examiner of proceedings finding before the U.S. Court of Appeals for the Federal Circuit regarding the Benitec Australia Ltd. v. Nucleonics, Inc. case and the European Patent Office regarding patent application no. EP19990910039. Benitec had requested the interview with the Examiner in the normal course of the Reexamination to discuss the response filed to the Office Action of 24 January 2007.

Next Steps
It is expected that the Examiner will review this new material and respond in a timely manner.

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About Benitec

Benitec is an Australian biotechnology company focused on licensing its extensive intellectual property portfolio and developing therapeutics to treat serious diseases using its proprietary ddRNAi technology. Its current therapeutic program is focused on Human Immunodeficiency Virus (HIV). For additional information, please visit www.benitec.com.

Docket No.: 023004.0013X1US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination of U.S. Patent No. 6,573,099:
Michael W. Graham et al.

Reexamination No.: 90/007247
Merged with No. 90/008096

Confirmation No.: 6310

Filed: October 4, 2004

Art Unit: 1639

For: GENETIC CONSTRUCTS FOR DELAYING OR REPRESSING THE EXPRESSION OF A TARGET GENE

Examiner: B. M. Celsa

DECLARATION OF INVENTOR IN *EX PARTE* REEXAMINATION

U.S. Patent and Trademark Office
Customer Window, MS Ex Parte Reexam
Randolph Building
401 Dulany Street
Alexandria, Virginia 22314

Dear Sir

I, Michael Graham, Ph.D., declare as follows:

1. I am a named inventor of the subject matter in the above-identified reexamination. I am a resident and citizen of Australia. During the period of December 1997 through the filing of the priority document for the patent under reexamination, I was a research scientist in Australia. During this period Robert Rice and Margaret Bernard were under my direction and supervision.

2. I have reviewed the above-identified reexamination, including the present claims. As I understand it, the presently claimed subject matter is generally directed to genetic constructs that are capable of delaying, repressing or otherwise reducing the expression of a target gene in an animal cell, as well as methods for using these constructs and animal cells comprising

these constructs. I understand that the presently claimed constructs comprise at least one structural gene sequence placed operably in a sense orientation under the control of a promoter and at least one structural gene sequence placed operably in an antisense orientation under the control of a promoter, where the structural gene sequences comprise a nucleotide sequence which is substantially identical to at least a region of a target gene, and where

a. the multiple structural gene sequences are placed operably under the control of a single promoter sequence, where optionally the structural gene sequences in sense and antisense orientations are spaced from each other by a nucleic acid stuffer fragment; or

b. the structural gene sequences in sense and antisense orientations are each placed operably under the control of individual promoter sequences.

3. I am aware of the rejections issued in an Office Action mailed January 24, 2007, in the pending reexamination. I understand that a rejection in the Office Action was based on the teachings of Fire U.S. Patent No. 6,506,559 (the "Fire reference"). The Fire reference was filed in late 1998, and claims priority to U.S. Serial No. 60/068,562 (the "Fire priority application") filed December 23, 1997, less than a year before the effective filing date of the patent under reexamination in the United States. It is my understanding that to show prior invention, the Examiner is requiring that I provide evidence of conception prior to the date of filing of the Fire priority application and then the Examiner is requiring that I show diligence from just before the filing date until reduction to practice or constructive reduction to practice of my own invention.

4. Exhibit 1 is a copy of laboratory notebook pages showing my preliminary work in plants. My early work on genetic constructs for reducing expression of a target gene was in plants and I spent significant amounts of time trying to produce such constructs. I consider this work important to my present invention because the layout of the constructs in plants was the basis for my later attempt in animals. This Exhibit was previously submitted in the June 12, 2006, 37 C.F.R. § 1.131 declaration. I conceived the subject matter of the presently claimed invention prior to December 23, 1997. Evidence for conception before the date of

the Fire priority application includes laboratory notebook pages 107 – 108, which show one of my first attempts to make a genetic construct which was designed to express both sense and antisense RNAs from multiple copies of a nucleotide sequence under the control of a promoter. Page 108 in particular shows my drawing of a "Hairpin GUS" construct that includes two copies of a structural gene sequence in the antisense and sense orientation, expression of which was driven by a single promoter. Laboratory notebook pages 110 – 121 show my additional experiments to build constructs with structural gene sequences in a sense and antisense orientation. Laboratory notebook pages 130 – 32 show experiments where I attempted to make expression cassettes containing two promoters designed to express separate sense and antisense RNAs. Laboratory notebook pages 138, 145, 147, 150, 151, 159, 169, 175, 181-192, 206, 216, 229 and 266 show experiments where I continued to try and create genetic constructs expressing separate sense and antisense RNAs. Laboratory notebook pages 138, 145, 150, 153, 158, 165, 168, 172, 175, 182, 185, 195, 197, 198, 200, 210, 227, 229, 240 and 254 show experiments where I developed constructs in which the structural genes were orientated in a sense and antisense orientation, some of which were controlled by separate promoters. I understand that this is evidence of a conception of genetic constructs of the same type as those of the claimed invention earlier than the priority date of Fire rather than the earliest conception of the claimed invention, which occurred before these notebook entries.

5. Further evidence of conception before the date of the Fire priority application includes the June 6, 1994 letter from CSIRO to John Slattery, as indicated in Exhibit 2. This Exhibit was previously submitted in the June 12, 2006, 37 C.F.R. § 1.131 declaration. In this letter, my employer at the time, CSIRO, requested from Mr. Slattery an opinion on the patentability of my new constructs that I believed would "be useful in mammalian systems", as I indicated on the last page of the attachment. Attached to the letter is my idea to create constructs such as the subject matter in the above-identified reexamination. For instance, the second figure, Case 2, is a construct comprising a single promoter that transcribes two structural gene sequences in an inverted repeat to form a transcript with a "hairpin" structure, where the inverted repeat is not separated by a stuffer fragment. This figure shows my idea of making a construct like the construct of Claim 3. The third figure, Case 3, is a construct comprising

two copies of a structural gene sequence, where one copy is placed operably in the sense orientation under the control of an individual promoter and the other copy is placed operably in the antisense orientation under the control of a separate promoter. Case 3 therefore shows my idea of making the construct of Claim 4 and indicates I had conceived of this invention on or before June 6, 1994.

6. Exhibit 3 is an early outline for a provisional patent application which I prepared on August 8, 1995. In this draft, I discuss decreasing gene expression in animals by use of novel transgene designs. This Exhibit was previously submitted in the June 12, 2006 37 C.F.R. § 1.131 declaration.

7. Exhibit 4 is a draft of an unpublished manuscript which I prepared on June 21, 1996. This Exhibit was previously submitted in the June 12, 2006, 37 C.F.R. § 1.131 declaration. I prepared this article for publication in a journal to try and demonstrate the widespread existence of an RNA degradative system in plants and other organisms based on a re-interpretation of the literature that existed at that time. While genetic constructs were not described in this document, their development was based on ideas presented therein, specifically I wished to design constructs to switch this RNA degradative system on more efficiently in transgenic organisms. I discussed evidence that this RNA degradative system existed in animals in the section titled "Post-transcriptional gene inactivation in other taxa" and believe this document demonstrates my thinking at that time, namely the types of constructs that might work in plants would also work in animals.

8. Exhibit 5 is a draft of a proposal I prepared on November 29, 1996, proposing that genetic constructs for gene silencing would prove effective in animals. This proposal was important because budgetary limits at Benitec (then called Ag-Gene and my research funder at that time) inhibited my ability to conduct all of the research I intended for target gene inactivation. In this proposal, I discuss the genetic constructs I previously created for plants and how I wanted to create "multiple gene constructs, the use of direct and inverted sequences and the design and use of RNA stabilizing sequences" to decrease gene expression in animals. When our funding increased, we promptly hired Robert Rice to work on post-transcriptional gene silencing in animal cells.

9. Exhibit 6 shows further evidence of my conception before the date of the Fire priority application and shows how I conceived a genetic construct design to express hairpin RNAs where the construct had a stuffer fragment inserted between the two copies of the nucleotide sequence, where one of the sequences was in a sense orientation and the other sequence was in an antisense orientation relative to the promoter. The first page of the exhibit is page 92 of the notebook of my assistant, M. Jobin. It is a June 6, 1997, entry describing--just below midpage--the use of the beta-glucuronidase (GUS) reporter sequence to insert between genes arranged in opposite orientation. On the second page of the exhibit, page 96 of M. Jobin's notebook dated June 13, 1997, M. Jobin describes using the GUS reporter sequence to insert between genes arranged in opposite orientation (see line 1) and also shows the synthesizer print-out for making GUS-1 and GUS-2 primers. Those print-outs are dated June 6 and June 10, 1997. The '099 patent describes using GUS as a specific marker gene at Col. 14, lines 1-34. I consider this Exhibit important because previously I had difficulty creating inverted repeat constructs without a stuffer fragment due to instability of such constructs in *E. coli*. The insertion of the stuffer fragment between the inverted repeat sequences allowed me to readily make such constructs, and as such I planned to incorporate this idea into the genetic constructs for reducing expression of animal genes. Thus, compared to constructs without a stuffer fragment, the inverted repeat constructs with a stuffer fragment were superior.

10. I understand the Examiner would like to see the diligence to reduce my invention to practice between the Fire priority date of December 23, 1997, and the '099 patent priority date of March 20, 1998. As such, I detail below the events that occurred. To assist the Examiner, I also include a calendar of December 1997, and January – March 1998.

December 1997

Su	Mo	Tu	We	Th	Fr	Sa
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27

28 29 30 31

7:◐ 13:○ 21:◑ 29:●

January 1998

Su	Mo	Tu	We	Th	Fr	Sa
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

5:◐ 12:○ 20:◑ 28:●

February 1998

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

3:◐ 11:○ 19:◑ 26:●

March 1998

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

5:◐ 12:○ 21:◑ 27:●

11. When Ag-Gene funding increased in late 1997, we promptly pursued hiring Robert Rice to work on preparing gene constructs for gene silencing in animal cells, corresponding to the designs I had conceived. From what I recall, we at Ag-Gene started discussing hiring Dr. Rice in October 1997. We wanted to work with Dr. Rice because he had extensive experience in a range of molecular biological techniques and plasmid design and construction. Dr. Rice's thesis topic was eukaryotic evolution and studying eukaryotic divergence using ribosomal RNA sequence data and secondary structure remodeling. As such, Dr. Rice also had experience with use of computers for systematic / bioinformatics analysis of DNA / RNA sequences.

12. On December 8, 1997, I decided to target the polymerase gene of the bovine enterovirus (BEV) as an exemplary target gene in animal cells. This gene was chosen because it could be easily determined whether the expression of constructs based on the gene had an effect on viral replication in animal cells. Specifically, since infection of Mabin Darby (MDBK) cells with BEV normally kills them, we could therefore determine whether expression of constructs in transformed cells might inhibit viral replication simply by determining whether

such transformed cells show prolonged survival following challenge with the virus under standardised conditions. Further, we knew that the BEV polymerase may be amplified using the polymerase chain reaction or alternatively, isolated using standard hybridisation techniques. With the assistance of Margaret Bernard ("Ms. Bernard"), I printed out the sequence of the polymerase gene of BEV, see Exhibit 7, page 2. (indicating the sequence was printed at 3:13pm on December 8, 1997). Again with the assistance of Ms. Bernard, I designed a pair of oligonucleotide primers to amplify a region of the BEV gene. These primers, designated BEV-1 and BEV-2 (pages 2-3 of Exhibit 7) were ordered by Ms. Bernard from a commercial supplier under my instruction on December 9, 1997. (*See, Id.* at 1, lower entry: the notation the primers were ordered December 9, 1998 is in error; they were ordered December 9, 1997 as evidenced by their entry on the notebook page of December 9, 1997 and their use on January 6, 1998). These primers were available for use by Ms. Bernard on January 6, 1998. We continued with BEV as a target gene all the way to actually practicing the invention, as can be seen in the figures in the patent application that we filed.

13. On or about December 8, 1997, I mentioned to Ms. Bernard that as soon as possible she would be devoting a greater amount of her time for work on a project with the new Research Scientist, Dr. Rice, in preparing the gene constructs for the animal target gene, in particular the constructs targeting BEV.

14. Dr. Rice arrived to commence employment on the "animal project" on December 21, 1997. On that day or the day after, I met with Dr. Rice and described to him in detail the types of constructs that I had envisaged for reducing expression of a target gene. The first type of construct was an inverted palindrome construct without a stuffer fragment. Claim 3 of my patent under this reexamination is to the inverted palindrome construct without the stuffer fragment and claim 7 is to a method of using the construct. The second type of construct was an inverted palindrome construct with a stuffer fragment. Claim 5 is to the inverted palindrome construct with the stuffer fragment and claim 9 is to a method of using the construct. Finally, I wanted to make a construct with two copies of a gene sequence where each copy was under the control of a separate promoter. Claim 4 is to this type of construct

and claim 10 is to a method of using this construct. On the days following, I had further discussions with Dr. Rice about these types of constructs.

15. The laboratory facilities of Ag-Gene were located at the Queensland Agricultural Biotechnology Centre (QABC), an operational centre of the Queensland State Government's Department of Primary Industries. The Queensland State Government provided paid leave for Christmas day (December 25), Boxing Day (December 26) and New Year's Day (January 1). Further, the Queensland State Government mandated that all State Government employees do not work on the days between December 26 and January 1. As such, the QABC laboratories and offices were closed from December 25, 1997 to January 1, 1998.

16. Dr. Rice and I met several times between December 21, 1997 and mid-January 1998 to discuss cosuppression in animal cells and the types of DNA constructs we wanted to prepare. We decided to build a range of constructs with the following structures: linear repeats, that is constructs containing a block of repeated DNA sequences in sense or in an antisense orientation; inverted repeats, that is constructs containing two inverted DNA sequences either with or without a DNA spacer sequence inserted between the inverted sequences; and a construct with two promoters expressing a sequence in the sense and antisense format.

17. From January 1998 to March 1998, Dr. Rice designed approximately 40 plasmid constructs. Exhibit 8 contains approximately 35 plasmid constructs he designed, most of which are also found as figures of the '099 patent.

18. When Ms. Bernard returned from her Christmas vacation on January 5 or 6, 1998, Dr. Rice and I informed her that we wanted her to prepare certain BEV constructs. We described the kind of constructs we wanted, namely the three constructs discussed above in paragraph 14. Ms. Bernard, with my assistance, was to start preparing the BEV constructs. *See*, Exhibit 7 at page 1. In the meantime, Dr. Rice was to use a computer program to design further genetic constructs. Dr. Rice and I explained to Ms. Bernard that the overall aims of the experiments were to "use Bovine enterovirus as a model system to study cosuppression in mammalian cells," which Ms. Bernard recorded in her laboratory notebook at page 2. Ms. Bernard took further notes from our talk, writing down the polymerase gene from BEV was

to be used as the sequence for the animal constructs. *Id.* Ms. Bernard states in her notes that once the constructs were prepared, she was going to "transfect mammalian cell line with constructs, probably using the Mabin Darby Bovine Kidney (MDBK) endothelial cell line." *Id.* The cells would then be challenged with BEV. *Id.* Ms. Bernard then describes the initial constructs. *Id.*

19. The first construct to be made was a BEV polymerase-GFP gene fusion in the vector pEGFP-N1. *Id.* In this arrangement, the CMV promoter of pEGFP-N1 lay upstream of the BEV sequence, while the EGFP sequence was placed downstream of and joined to the BEV sequence. Both the BEV and EGFP sequences were designed to be transcribed conjointly by the CMV promoter. The GFP domain was to be used as a marker to indicate BEV-pol positive cells lines and determine whether cosuppression could be detected by transient transfection of BEV-pol positive cells with GFP cDNA. The next construct was similar to the BEV polymerase-GFP fusion construct above, except that the EGFP sequences would be removed and only the BEV sequence would be transcribed from the CMV promoter. *Id.* The next construct describes the use of double promoter constructs (*i.e.*, having two promoters) with the BEV sequence being expressed in sense and antisense format.

20. The January 7, 1998 entry demonstrates Ms. Bernard was cloning the BEV polymerase gene into the carrier plasmid vector pCR2.1. *Id.* at pages 2 – 7. I planned to have her to clone the BEV polymerase gene into pCR2.1, which was the first step of making the BEV polymerase-GFP fusion in the vector pEGFP-N1. Once the BEV polymerase-GFP fusion was in the pEGFP-N1 vector, we planned to use a BglII/BamHI cloning strategy that would result in two alternative fusion constructs where the BEV gene sequence would be cloned in the sense or antisense orientation. Dr. Rice and I believed that once we had the two fusion constructs, we could easily insert the second copy of the BEV gene sequence in the sense and/or antisense orientation into the constructs. This was an element in making the constructs we later claimed in the '099 patent.

21. The primers BEV-1 and BEV-2 were used to PCR amplify the BEV polymerase gene sequence, corresponding to a DNA fragment of about 1.4 kilobases. We then cloned the PCR product into the pCR 2.1 plasmid vector. *Id.*

22. The January 8, 1998 entry demonstrates Ms. Bernard continued the work of January 7, 1998. *Id.* at page 8.

23. The January 9, 1998 entry demonstrates Ms. Bernard continued the work of January 7, 1998. *Id.* at pages 8 – 9.

24. January 10, 1998 was a Saturday and the laboratory was closed.

25. The January 11 and 12, 1998 entry demonstrates Ms. Bernard took steps to grow the clones obtained for the invention. *Id.* at page 9.

26. The January 13, 1998 entry demonstrates Ms. Bernard took further steps to clone BEV into the PCR2.1 and pEGFP. *Id.* at page 10. Further, Ms. Bernard describes how she validated the successful cloning of the BEV polymerase gene sequence into pCR2.1 and confirmed this by endonuclease restriction mapping. *Id.*

27. The January 14 – 16, 1998 entry demonstrates Ms. Bernard took steps to the make the BEV polymerase-GFP fusion in the vector pEGFP-N1. *Id.* at pages 11 – 14. Specifically, Ms. Bernard used a *Bgl*II/*Bam*H1 cloning strategy that resulted in two alternative fusion constructs where the BEV gene sequence was cloned in the sense or antisense orientation. *Id.* As previously mentioned, the BglII/BamH1 cloning strategy that results in two fusion constructs which could be used to easily insert the BEV gene sequence in the sense and/or antisense direction into other constructs.

28. January 17 – 18, 1998 was a Saturday and Sunday and the laboratory was closed.

29. The January 19 – 20, 1998 entry demonstrates Ms. Bernard continued the work of January 14 – 16, 1998. *Id.* at pages 14 – 16.

30. The January 21- 23, 1998 entry demonstrates Ms. Bernard used PCR to check for the presence of the BEV insert. *Id.* at pages 16 – 19. Ms. Bernard drew three diagrams depicting the location of the primers and the expected orientation of the BEV DNA sequence for each PCR product. *Id.* Unfortunately, Ms. Bernard encountered problems and the results were not

as expected. *Id.* at page 17. We discussed the matter and agreed that she should try to clone the BEV polymerase gene sequence into the pEGFP-N1 again.

31. The January 21, 1998 entry demonstrates Dr. Rice used a software program to finalize his computer designs of pCR.Bgl.GFP.Bam, pCMV.Virus and pCR2.1, which I believed important to continue development. *See,* Exhibit 8 at pages 1 – 3.

32. As the January 22, 1998 entry demonstrates, Dr. Rice finalized the designs of the constructs pCMV.BEV.2, pCMV.BEVnt, pCMV.BEV.GFP.VEB, pCMV.VEB, pEGFP.BEV.1, pCMV.BEV.VEB, and pCMV.BEVx2 which I believed important to continue development of the invention. *See*, Exhibit 8 at pages 4 – 10. Dr. Rice and I were pleased with these designs. The idea we had was that once Ms. Bernard cloned the BEV polymerase gene sequence into the pEGFP-N1, we could construct pCR.BEV.2. Construction of the pCR.BEV.2 was important to reducing the invention to practice because it could be used to form the constructs we had conceived corresponding to our claims.

33. For example, in one plan we wanted to sub-clone the BEV sequence from the pCR.BEV.2 in the antisense orientation, thus producing the plasmid, pCMV.BEV.VEB. The pCMV.BEV.VEB construct comprises an inverted palindrome of BEV under the control of one promoter. As such, this construct would fall within at least claim 3. This construct is also presented schematically as Figure 14 of the '099 patent. We also wanted to make the above plasmid pCMV.BEV.GFP.VEB. This plasmid comprises an inverted palindrome of the BEV sequence under the control of one promoter with GFP as a stuffer fragment. As such, this construct would fall within at least claim 5. To make this plasmid, we would subclone the GFP from pCR.Bgl.GFP.Bam into pCMV.BEV.2 to produce pCMV.BEV.GFP. We then planned to insert the second BEV sequence in an antisense orientation. The resulting plasmid, pCMV.BEV.GFP.VEB, is presented schematically as Figure 15 of the '099 patent.

34. January 24 and 25, 1998 was a Saturday and Sunday and the laboratory was closed.

35. The January 26 – 28, 1998 entry demonstrates Ms. Bernard again attempted to clone the BEV polymerase gene sequence into pEGFP-N1. Exhibit 7 at pages 20 – 24.

36. From January 29 – February 1, 1998, the transformed cells were allowed to grow.

37. The February 2, 1998 entry demonstrates that the results of the transformation were analyzed and new ligations were set up. *Id.* at pages 25 – 26. Ms. Bernard again encountered problems. As page 25 of Ms. Bernard's notebook indicated, I discussed the results with her, and recommended she try again but instead amend the method. As such, Ms. Bernard again set up experiments to clone the BEV polymerase gene sequence into pEGFP-N1. *Id.* at page 26.

38. Ms. Bernard allowed the DHSα chemically competent cell grow on February 3, 1998. *Id.* at page 37.

39. The February 4 – 6, 1998 entry demonstrates ligations were transformed into the DHSα chemically competent cells. *Id.* at pages 27 – 30. The transformants were then PCR screened. *Id.* at page 30.

40. February 7, 1998 was a Saturday and the laboratory was closed.

41. The February 8 – 11, 1998 entry demonstrates Ms. Bernard's experiments continued. *Id.* at pages 31 – 36. We were pleased to find that Ms. Bernard succeeded in obtaining a fusion clone. *Id.* at page 33. As such, Ms. Bernard went on to sequence the fusion clone to confirm the sequence was in the clone. *Id.* at page 36. Further, Ms. Bernard hand drew a diagram depicting the location of the primers and expected orientation of the BEV-GFP sequence. *Id.*

42. February 14 – 15 was a Saturday and Sunday and the laboratory was closed.

43. Now that we had prepared the fusion clone, we were ready to take the next step. The February 17, 1998 entry demonstrates Ms. Bernard started cloning four new constructs, namely the constructs pCR.BEV.2, pCR.BEV.3, pCR.BamGFPBglII, and pCMV cass. *Id.* at

pages 37 – 39. pCR.BEV2 was a construct comprising BEV-pol that could later be used to prepare expression constructs in a sense orientation, or alternatively in an antisense orientation. As previously stated, pCR.BEV2 was an element of reducing the invention to practice because it could be used to form the constructs of our claims, including the pCMV.BEV.VEB construct which comprises an inverted palindrome of BEV under the control of one promoter. The pCMV.BEV.VEB construct falls within at least claim 3. This construct is also Figure 14 of the '099 patent. pCR.BEV2 was also used to make the plasmid pCMV.BEV.GFP.VEB, which contained an inverted palindrome of BEV under the control of one promoter with GFP as a stuffer fragment. As such, this construct would fall within at least claim 5. Ms. Bernard also started to clone pCR.BEV3, a construct comprising an untranslatable BEV-pol. Ms. Bernard also started to clone pCRBamGFPBgIII, which is a construct comprising a stuffer for use in interrupting BEV-pol sense and BEV-pol antisense in a hairpin construct. The EGFP sequence was selected as a stuffer because it would be useful for determining whether the stuffer could mediate post transcriptional gene silencing. The GFP is flanked by the BamHI and BglII restriction sites, so the GFP would be easy to remove. We planned to use this in our constructs that contained an inverted palindrome with a stuffer, such as pCMV.BEV.GFP.VEB discussed above. Ms. Bernard also started to clone pCMV.cass, which is plasmid pEGFP-N1 except that the EGFP gene sequence has been removed. We chose pCMV.cass as a basic plasmid expression cassette for future clones, and to later make constructs such as pCMV.BEV.SV40L.VEB, which comprises a BEV polymerase placed in the sense orientation to one promoter and another BEV polymerase placed in the antisense orientation to another promoter.

44. The February 18 – 20, 1998 entry demonstrates Ms. Bernard continued her work toward making a BEV polymerase-GFP fusion construct. *Id.* at pages 40 – 41.

45. February 21 and 22 were Saturday and Sunday and the laboratory was closed.

46. The February 23 – 24, 1998 entry demonstrates Ms. Bernard continued the experiments of the previous week. *Id.* at pages 42 – 45. Notably, she identifies the putative fusion clone (#61). *Id.* at page 44.

47. The February 25, 1998 entry demonstrates Dr. Rice designed the construct of pCMV.Lac, the diagram of which is figure 25 of the '099 patent. Exhibit 8 at page 11. Dr. Rice also designed the construct of pCMV.LAC1.pla. *Id.* at page 12.

48. On February 26, 1998, under my and Dr. Rice's direction, Ms. Bernard started to clone pCR.BEV2, pCR.BEV3 and pCR.BamGFPBgl by setting up PCR to amplify fragments for the new constructs. Exhibit 7 at page 46. As previously mentioned, I wanted to obtain pCR.BEV2 to make the constructs of our claims, including the plasmid pCMV.BEV.VEB construct, which comprises an inverted palindrome of BEV under the control of one promoter, and the plasmid pCMV.BEV.GFP.VEB, which contained an inverted palindrome of BEV under the control of one promoter with GFP as a stuffer fragment. These constructs correspond to at least claims 3 and 5, respectively.

49. On this same day, Dr. Rice designed the construct of pCMVLac1.OPRSV1.cass, the diagram of which is Figure 26 of the '099 patent. Exhibit 8 at page 13. On this same day Dr. Rice also designed the construct of pCMVLac1.OPRSVL.GFP. *Id.* at page 14.

50. The February 27, 1998 entry demonstrates Ms. Bernard continued her cloning of pCR.BEV2, pCR.BEV3 and pCR.BamGFPBgl. Exhibit 7 at page 47. On this same day, Dr. Rice designed the constructs of pCMVLac1.OPRSV1.GFP.cass and pCMV.TYRLIB, the diagrams of which are figures 27 and 24, respectively, of the '099 patent. Exhibit 8 at pages 15 – 16. Dr. Rice also designed the construct pCMVLac.OPRSVL.GFP.TYR. *Id.* at page 17.

51. February 28 and March 1, 1998 were Saturday and Sunday and the laboratory was closed.

52. The March 2, 1998 entry demonstrates Ms. Bernard continued her work to clone the constructs of pCR.BEV2, pCR.BEV3 and pCR.BamGFPBgl. Exhibit 7 at page 48. On this same day, Dr. Rice designed the construct of pCMV.TYR, the diagram of which is figure 23 of the '099 patent. Exhibit 8 at page 18.

53. The March 3 – 5, 1998 entry demonstrates Ms. Bernard continued her work to clone the constructs of pCR.BEV2, pCR.BEV3 and pCR.BamGFPBgl. Exhibit 7 at pages 49 – 52.

Notably, Ms. Bernard confirmed the sequence of the clone on page 50 of the laboratory notebook and the PCR screened the clones on page 51 – 52.

54. The March 5, 1998 entry demonstrates Dr. Rice designed the constructs of pCMV.O.SV40L.BEV, pCMV.O.SV40L.VEB, pCMV.BEV.SV40L.O, pCMV.BEV.SV40L.R, pCR.BEV.1, pCR.BEV.2, pCR.BEV.3, pCR.SV40L, the diagrams of which are figures 17, 18, 16, 22, 6 – 8 and 4, respectively, of the '099 patent. Exhibit 8 at pages 19 – 22, 24 – 29. On this same day, Dr. Rice also designed the construct of pCR.Bgl.GFP.Bam. *Id.* at page 23.

55. The March 6, 1998 entry demonstrates Ms. Bernard ligated the amplified fragment into pPCR 2.1 to obtain pPCR2.1 EGFP. Exhibit 7 at pages 53 – 54. This was then cut with BamH1 and BglII to provide a fragment, that was used to prepare a hairpin construct pBEV2.EGFP.VEB2.

56. On this same day, Dr. Rice designed the constructs of pCMV.cass, pCMV.SV40L.cass, pCMV.SV40LR.cass, pCMV.BEV.SV40L.BEV, pCMV.BEV.SV40L.VEB, the diagrams of which are figures 2, 5, 21, 19, and 20, respectively, of the '099 patent. Exhibit 8 at pages 29 – 33. On this same day, Rice also designed the construct of pCMV.BEV.SV40L.R.cass, pEGFP.N1MCS. *Id.* at page 34.

57. We were excited about the design of the plasmid pCMV.BEV.SV40L.VEB because this plasmid comprises a BEV polymerase placed in the sense orientation to one promoter and another BEV polymerase placed in the antisense orientation to another promoter. This plasmid therefore is an isolated construct of at least claim 4, and indeed corresponds to Figure 20 of the '099 patent. To make this construct, we planned to make a pCMV.SV40L.cass plasmid by sub cloning pCR.SV40L into pCMV.cass, and then insert the BEV polymerase from Ms. Bernard's pCR.BEV.2 into the sense orientation to make pCMV.BEV.SV40L.O. The BEV polymerase from pCR.BEV.2 would then sub cloned into the antisense orientation into the pCMV.BEV.SV40L.O to make pCMV.BEV.SV40L.VEB.

58. In anticipation of making the pCMV.BEV.SV40L.VEB clone, on March 18, Ms. Bernard started preparing the pCMV.cass construct. Exhibit 7 at page 66.

59. March 7 – 8, 1998 was a Saturday and Sunday and the laboratory was closed.

60. The March 9 – 11, 1998 entry demonstrates Ms. Bernard prepared larger amounts of DNA for mammalian cell transfections, including pEGFP.BEV1 and pEGFP-N1. Exhibit 7 at pages 55 – 60. Further, the MDBK cells were split in preparation for transformation on Monday, March 9, 1998. Exhibit 9 at page 1.

61. The March 11, 1998 entry demonstrates I transfected Mabin Darby Bovine Kidney (MDBK) endothelial cells with the pEGFP.BEV.1 constructs. Exhibit 9 at pages 1 – 2.

62. The March 12 – 13, 1998 entry demonstrates Ms. Bernard and I continued our respective experiments. *Id.* at 3; exhibit 7 at pages 61 – 62.

63. March 14 – 15, 1998 were a Saturday and Sunday and the laboratory was closed.

64. The March 16, 1998 entry demonstrates Ms. Bernard obtained the putative clones for pCR.BEV2 and pCR.BEV3. Exhibit 7 at page 63. On this day, I continued my transfection experiment. Exhibit 9 at page 3.

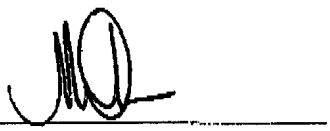
65. The March 17, 1998 entry demonstrates Ms. Bernard confirmed the clones had the proper insert. Exhibit 7 at page 64. As Ms. Bernard stated, the next experiments were to sequence clones with universal forward and reverse primers. *Id.* On this same day, I conducted kill curves for the Mabin Darby Bovine Kidney cells and started selection of constructs. Exhibit 9 at page 4.

66. From March 18 – 19, 1998, Ms. Bernard confirmed the pCR.BEV2 and pCR.BEV3 clones by sequencing. Exhibit 7 at page 67. Further, Ms. Bernard prepared the pCMV.cass construct. *Id.* at pages 65 – 66, 68.

67. The March 20, 1998 entry demonstrates Ms. Bernard continued with transformation of colonies. *Id.* at page 68. The expression cassette pCMV.cass was later confirmed by sequencing. On this same day, I continued my kidney cell transfection experiments. Exhibit 9 at page 5.

68. After this reduction to practice, I filed a patent application in Australia that was the basis for and was claimed as priority by the patent under reexamination.

69. I declare that all statements made of my own knowledge are true and all statements made on information and belief I believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent.



7 March 2008

Michael Graham Date