

DECLARATION OF TERRY HERMISTON
IN RELATION TO PCT PATENT APPLICATION PUBLICATION
NUMBER WO2015/059303 (PCT/EP2014/072919)

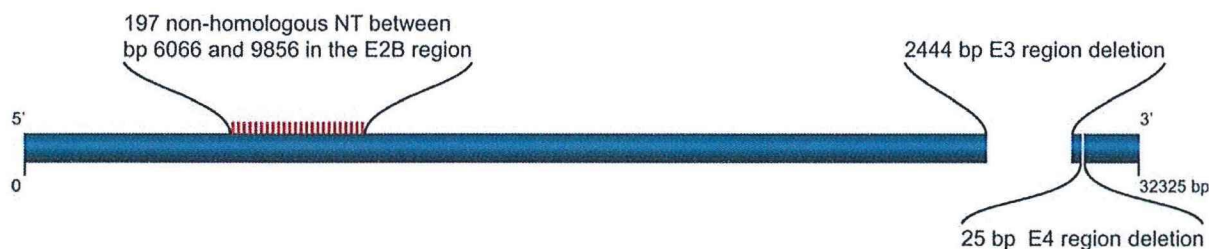
I, **Terry Hermiston**, in relation to the claimed subject matter in the above-referenced application, declare that:

1. I am not named as an inventor on the above identified application. However, I have considerable expertise in the technical field of the subject-matter of the application. I have been asked to comment from a technical and scientific perspective. I was one of the first in the field to work on oncolytic viruses. I was also part of the group that created the oncolytic virus now known as EnAd (enadenotucirev) and formerly known as ColoAd1. My *Curriculum Vitae* is attached to this declaration.
2. I have worked in pharmaceutical companies in the field of gene technologies and in particular therapeutic viruses for more than 18 years. My current role is Vice President, Head of Biologics Research US at Bayer. I have equity in the company PsiOxus Therapeutics Ltd, which owns application WO2015/059303
3. The subject of the present application is an oncolytic replication competent group B adenovirus comprising a transgene encoding a “therapeutic protein or RNA molecule” located between the fiber (L5) and the E4 region.
4. Surprisingly the inventors have established a location in EnAd where complicated therapeutic molecules such as antibodies can be inserted robustly and consistently to provide a stable virus, with infectivity and a replicative cycle (i.e. a potency) approximately equal to or greater than the parent virus. The data in the case shows the viruses are able to selectively infect the tumor cell and once inside the cell the virus

expresses the “therapeutic protein”.

5. I have been given an amended claim for the above-identified application, the Written Opinion of the International Preliminary Examining Authority and I have been given the prior art documents **D1** (WO2005/118825), **D2** (Kuhn *et al*), **D3** (WO2006/060314), **D4** (WO2005/086922), **D5** (Alexa *et al*), **D6** (Dias *et al*), **D7** (Hermiston), **D8** (Lotta) and **D9** (WO2005/107474).
6. I am familiar with the documents **D1**, **D2**, **D3**, **D6** and **D7** because I am named as an inventor on **D1**, **D3** and **D6** and I am named as an author on **D2** and **D7**. **D1** is the original patent application describing chimeric oncolytic adenoviruses. A bioselection process was used to generate the oncolytic viruses. This process is discussed in Kuhn (**D2**) on page 2 col 1 under the heading “*Directed Evolution of pooled adenovirus serotypes on different tumor cell lines derived distinctly different viral pools that are superior to the potency of Ad5*”.
7. The virus of SEQ ID NO: 1 in **D1** is the oncolytic adenovirus ColoAd1 (now referred to as EnAd). This virus is characterized as a group B adenovirus because it has a fiber and hexon of a group B virus. It is derived from Ad11p, the so-called Slobitski strain. It has deletions in the E3 region and in E4orf4. It also has a chimeric E2B region derived from Ad3 and Ad11. Figure 2 on page 5 of Kuhn (**D2**) illustrates this:

ColoAd1



8. This virus EnAd (ColoAd1) showed an increased therapeutic activity relative to the parent adenovirus Ad11. This is also discussed in Kuhn (**D2**) at the bottom of page 2 col

2. EnAd is currently in clinical trials for the treatment of epithelial cancers, in particular colorectal cancer.
9. **D1** envisages that a transgene may be incorporated into the virus genome but no further technical details are provided in **D1** as to how and where to insert the gene.
10. Prior to filing the case WO2006/060314 (**D3**) those skilled in the art had generally deleted E1 and/or E3 regions of the virus and then inserted in the transgene in one or both of these locations. This technique was fine for viral vectors but was fairly limited for replication competent viruses because the E1 region was required. In replication competent viruses the E3 region could be deleted and space created could be filled by a transgene (i.e. in the E3 region).
11. This strategy relied on detailed knowledge of the virus genome and at the time, and even today to some extent, most of the work had been performed on the group C adenovirus Ad5.
12. Kuhn (**D2**) published in 2008 states on page 1 col 2:
"..alternative human Ad serotypes to the well studied Ad5 serotype have been ignored"

D3 page 1 and 2 also describe this issue:

The incorporation of therapeutic transgenes into an oncolytic virus is a complex process. The insertion event needs to occur in a site that maintains the replication competence of the viral agent, which is complicated as viruses maximize their coding capacity by generating highly complex transcription units controlled by multiple promoters and alternative splicing (Akusjarvi and Stevenin (2003) *Curr. Top. Microbiol. Immunol.* 272:253-286). Consequently, the choice of insertion sites for therapeutic genes has been limited primarily to regions known to be non-essential for viral DNA replication *in vitro* (Hawkins et al. (2001) *Gene Ther.* 8:1123-1131; Kurihara et al. (2002) *J. Clin.*

Invest. 106:763-771) or by the replacement of a deleted region of the viral genome to create the oncolytic virus (Freytag et al. (1998) *Human Gene Ther.* 9:1323-1333; Lee et al. (2001) *Cancer Gene Ther.* 8:397-404). While these approaches allow for therapeutic gene insertion and expression, they are dependent upon a high level of understanding of the viral biology (i.e. sites non-essential for viral replication), a known viral genome sequence (for use in genetic engineering or utilization of endogenous restriction enzyme sites) and the presence of molecular biology systems for genomic manipulations that may not be currently available for non-Ad5-based systems.

13. The work we did in **D3** gave us the ability to scan the viral genome for locations which are capable of accepting a transgene without the requirement for prior structural knowledge of the virus genome. This was achieved by using a mutated Tn7 transposon described in WO98/37205. This modified transposon does not have a predetermined bias for locations where it can insert itself in the genome of the virus. When you attach a transgene/ transgene cassette to the transposon, the system itself finds a suitable location for insertion. Only viable viruses survive the process, which reduces the amount of screening required to find viruses where genes have been successfully inserted.
14. Even though the transposon was non-biased we found the location and orientation of the insertion was to some extent influenced by the properties of the transgene and/or regulator elements associated therewith, such as the promoter. In the work we did in Ad5 once a gene was inserted in a particular location then sometimes it was difficult to replace this gene with another gene. In one instance, for example we did not get what was expected when we tried to replace the GFP gene inserted into the Ad5 genome with a luciferase gene. The luciferase gene inserted itself in a different orientation, which of course can affect how the gene is expressed. The expression machinery (endogenous or exogenous) and the transgene significantly influenced the acceptance site and with it, the relative timing and level of expression and the ability of the virus to replicate to levels equivalent to the parent from which it was derived.
15. At that time although we thought that a single orientation may be consistently superior

for a given site, what we showed was that the orientation effects within the Ad genome, the highly complex nature of the Ad transcription machinery, and the unusual context of the newly identified gene insert sites made gene expression levels difficult to predict.

16. Whilst the non-biasedly inserting transposon work in **D3** was a real advancement because it gave us a method and tools for potentially identifying suitable locations within the genome for inserting genes in replication competent adenoviruses it did not help us predict, without doing the experiment, what would be suitable locations for the insertion.
17. Kuhn (**D2**) in was published in 2008 and on page 6 in relation to EnAd (ColoAd1) it states:

Armed oncolytic viruses seek to complement the potency of the oncolytic virus by the addition of therapeutic transgenes [20]. In this approach it is important that a therapeutic transgene insertion site within the viral genome be identified that does not compromise the life cycle and therefore the potency of the virus. Unlike Ad5, where the biology and description of insertion sites compatible with the viral life-cycle are well described, ColoAd1 represents a novel agent that is primarily derived from the poorly studied Ad11p genome. Consequently, a transposon-based system that can scan the genome for insertion sites in a non-prejudiced fashion was utilized for the identification of compatible transgene insertion sites [27]

18. In Kuhn (**D2**) although we state that the green fluorescent protein gene was inserted at random sites throughout the ColoAd1 genome, we did not specify where this was and no sequence information for these constructs was provided. Thus Kuhn (**D2**) does not give you any guidance about what are suitable locations for inserting genes in group B viruses. The disclosure of Kuhn (**D2**) is simply a method for determining a suitable location. What is more even if Kuhn (**D2**) had provided the specific locations the technology disclosed therein was such that the site identified was suitable for the specific construct of the transgene/transgene cassette used. Employing a different transgene/transgene cassette may ultimately change the location of insertion into the viral genome. Furthermore, it

was not necessarily possible to change the transgene after insertion by replacing it with another gene.

19. In **D3** most of the work we did was the group C adenovirus Ad5. Example 9 in **D3** does describe insertion of a transgene (GFP under control of the exogenous promoter SV40) into the group B virus, EnAd and replacing the GFP insert with a different transgene thymidine kinase (TK) under control of the exogenous TK promoter. But the specific locations of the transgenes is not provided.
20. Group C viruses, such as Ad5 are significantly different from group B adenoviruses, such as EnAd. For example group B adenoviruses, such as EnAd, infect cells via either the CD46 or DSG2 receptors as opposed to infecting cells through the CAR receptor. The EnAd virus seems to replicate rapidly, which may contribute to its beneficial properties.
21. We had done work on Ad5 in **D3**, however based on this work we could not predict what locations would be suitable in group B viruses, such as EnAd, because of the different mechanisms and properties of these viruses.
22. The expression in a cancer cell is an important point because we did not know whether a cancer cell could be made to express a recombinant protein.
23. The number of elements that needed to come together to make the viruses of the present disclosure are significant from a scientific perspective. To date we don't fully understand from which structural features of the virus the oncolytic properties of the virus are derived. This limits to some extent the amount of "rational" design that can be applied to these entities.
24. The disclosure of **D4** relates to a conditionally replicating adenovirus mutated in the E1A region, wherein the mutation prevents binding to the retinoblastoma (Rb) protein and inactivation of the Rb pathway. The exemplified virus $\Delta 24$ is derived from the group C virus Ad5 by deleting part of the E1A region. This mutation increases the oncolytic

activity of the virus.

25. The viruses of **D4** may be armed. The specifications indicate that the E3 region is suitable for the insertion of the transgene. As I read it, the use of an exogenous promoter is envisaged for the transgene. In Examples such as Example 5 the E3 region is deleted in $\Delta 24$ and a transgene is inserted in its place under the control of an exogenous promoter.
26. Thus **D4** employs known techniques for adenoviral vectors to insert a transgene, as discussed above in paragraph 10. I don't see any technical disclosure in **D4** describing new positions or suggesting other locations where transgenes may be inserted in replication competent adenoviruses.
27. **D5** is a paper describing an oncolytic vaccinia virus comprising an anti-VEGF transgene. Vaccinia is a member of the Poxviridae family of viruses. It is a large double stranded DNA genome and the viral particle is enclosed in an envelope protein. The structure of Vaccinia is different to adenoviruses, not least because adenoviruses do not have an envelope protein. **D5** tells me that a transgene under the control of an exogenous promoter has been successfully incorporated into a replication competent oncolytic Vaccinia virus. **D5** does not teach me how and where to insert a transgene into a replication competent oncolytic group B adenovirus.
28. As discussed above I am named as an inventor on **D6**, which relates to the non-biasedly inserting transposon work. As discussed above this disclosure is a method for finding suitable locations within the genome for insertion of transgenes.

29. **D7** is one of my early papers expounding the benefits of arming replication selective viruses. At that time we had not created ColoAd1 (EnAd) and my focus was the Ad5 derived virus ONYX-015, which needs dysregulation of p53 in tumor cells to replicate. **D7** does not describe or suggest a location between L5 and E4 for inserting a transgene into a replication competent oncolytic group B adenovirus.
30. **D8** is an academic dissertation on the subject of "Improving Oncolytic Adenoviral Therapies for Gastrointestinal Cancers and Tumor Initiating Cells". It attempts to summarize what was known about the adenoviruses and stimulate discussion on how to improve them. I've not read all of this document because it is about 70 pages. However, it does not appear to teach or suggest a location between L5 and E4 for inserting a transgene into a replication competent oncolytic group B adenovirus.
31. **D9** relates to oncolytic adenovirus comprising an adenovirus death protein wherein part or all of the E3 region is deleted. Group C viruses, such as Ad5 comprise adenovirus death protein. Group B viruses, such as ColoAd1 (EnAd) do not encode an adenovirus death protein. The group B viruses work by a different mechanism. D9 does not appear to teach or suggest a location between L5 and E4 for inserting a transgene into a replication competent oncolytic group B adenovirus.
32. All statements made herein of my own knowledge are true, and I believe that all statements of information and opinion are true. I made these statements with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing from the application.

Signature: 

Date: 12/01/2015

Dr. Terry Hermiston

Curriculum Vitae

Scientific Degrees:

B.S., Iowa State University – 1983
Ph.D., University of Iowa - 1989

Professional Experience

Dec 2010 – Present

**Site Head, US Innovation Center, Bayer
Healthcare Pharmaceuticals, Mission Bay**

Dec 2008 – Present

**Vice President, Biologics Research, Bayer
Healthcare Pharmaceuticals, Inc.**

May 2007 – Dec 2010

**Site Head, Bayer Healthcare Pharmaceuticals,
Inc., Richmond**

November 2006 – May 2007

**Director of Biologics Target Discovery, Bayer
Healthcare Pharmaceuticals, Inc.**

October 2000 – November 2006

**Principal Scientist/Scientific Director,
Department of Gene Therapy Research/Gene
Technologies, Berlex Biosciences, Schering AG,**

May 1996 – October 2000

**Scientist/Associate Director, Oncolytic Virus
Research, Onyx Pharmaceuticals**

Editorial and Reviewer Roles:

- ◆ Editor, yearly edition dedicated to Gene Transfer and Cell-Based Therapies, *Current Opinion in Molecular Therapeutics* (2002-2010)
- ◆ Ad Hoc Reviewer for national and international grant committees including:
 - NIH AIDS-associated Opportunistic Infections and Cancer Study Section, Program Project Grant review committee (2003-7)
 - Israel Science Foundation (2004)
 - NIH Delivery Systems and Nanotechnology Study Section (2005)
- ◆ Member of the organizing committee for the International Conference on Oncolytic Viruses (2005-2008)
- ◆ Member of the ASGT Educational Committee (2006-2008)

Membership in Scientific Organizations

- ◆ The American Society for Microbiology, 1984 – present
- ◆ American Association of Cancer Researchers, 1998 – present
- ◆ American Society of Gene Therapy, 2000 – present

Board of Directors Appointments

- ◆ Member of the Board of Directors, California Healthcare Institute, 2010 – present
- ◆ Member of the Board of Directors, Jennerex Biopharmaceuticals Inc., 2011- present

Professional Training

- ◆ The Global Institute for Leadership Development (GILD) Training, Drs. Phil Harkins and Marshall Goldsmith, Instructors (2002)
- ◆ Project Management Training (Project Management for Research, Team Effectiveness, Negotiation and Problem Solving for Project Managers) (2003)
- ◆ Creativity and Innovation in the Organization – UCLA Anderson School of Management, Dr. Moshe Rubenstein, Instructor (2004)
- ◆ Management of Technology and Innovation – California Institute for Technology (Caltech), Dr. Ralph Katz, Instructor (2004)
- ◆ Building Global Leadership (BGL) – Fuqua School of Business, Duke University, R. David Thomas Center and Schering University, Potsdam, Germany, Dr. Dan Laughhunn and Dr. Liz Mellon, Instructors (2005)

ORIGINAL RESEARCH PAPERS

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2. **Hermiston, TW**, Malone, CL, Stinski, MF. 1990. Human cytomegalovirus immediate-early two protein region involved in negative regulation of the major immediate-early promoter. *J. Virol.* 64: 3532-3536, 1990.
3. Liu, B, **Hermiston, TW**, Stinski, MF. 1991. A cis-acting element in the major immediate-early (IE) promoter of human cytomegalovirus is required for negative regulation by IE2. *J. Virol.* 65: 897-903.
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6. **Hermiston TW**, Hellwig R, Hierholzer JC, Wold, WS. 1993. Sequence and functional analysis of the human adenovirus type 7 E3-gp19K protein from 17 clinical isolates. *Virology* 197: 593-600.
7. Shisler J, Duerksen-Hughes, P, **Hermiston, TW**, Wold WS, Gooding, LR. 1996. Induction of susceptibility to tumor necrosis factor by E1A is dependent on binding to either p300 or p105-Rb and induction of DNA synthesis. *J. Virol.* 70: 68-77.
8. Tollefson, AE, Scaria, A, **Hermiston, TW**, Ryerse, JS, Wold, LJ, Wold, WS. 1996. The adenovirus death protein (E3-11.6K) is required at very late stages of infection for efficient cell lysis and release of adenovirus from infected cells. *J. Virol* 70: 2296-2306.
9. Sparer, TE, Tripp, RA, Dillehay, DL, **Hermiston, TW**, Wold, WS, Gooding, LR. 1996. The role of human adenovirus early region 3 protein (gp19K, 10.4K, 14.5K and 14.7K) in a murine pneumonia model. *J. Virol.* 70: 2431-2439.
10. Tollefson, AE, Ryerse, JS, Scaria, A, **Hermiston, TW**, Wold, WS. 1996. The E3-11.6-kDa adenovirus death protein (ADP) is required for efficient cell death: characterization of cells infected with adp mutants. *Virology* 220: 152-162.
11. Krajcsi, P, Dimitrov, T, **Hermiston, TW**, Tollefson, AE, Ranheim, TS, Vande Pol SB, Stephenson, AH, Wold, WS. 1996. The adenovirus E3-14.7K protein and the E3-10.4K/14.5K complex of proteins, which independently inhibit tumor necrosis factor (TNF)-induced apoptosis, also independently inhibit TNF-induced release of arachidonic acid. *J. Virol.* 70: 4904-4913, 1996.

12. Dimitrov, T, Krajcsi, P, **Hermiston, TW**, Tollefson, AE, Hannink, M, Wold, WS. 1997. Adenovirus E3-10.4K/14.5K protein complex inhibits tumor necrosis factor-induced translocation of cytosolic phospholipase A2 to membranes. *J. Virol.* 71: 2830-2837.
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15. Kirn, D, **Hermiston, T**, McCormick F. 1998. ONYX-015: clinical data are encouraging. *Nat. Med.* 4: 1341-1342.
16. Heise, C, **Hermiston, T**, Johnson, L, Brooks, G, Sampson-Johannes, A, Williams, A, Hawkins, L, Kirn, D. 2000. An adenovirus E1A mutant that demonstrates potent and selective systemic anti-tumoral efficacy. *Nat Med* 6: 1134-1139.
17. Shen, Y, Kitzes, G, Nye, JA, Fattaey, A, **Hermiston, T**. 2001. Analyses of single-amino-acid substitution mutants of adenovirus type 5 E1B-55K protein. *J. Virol.* 75: 4297-4307.
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20. Hawkins, LK, and **Hermiston, T**. 2001. Gene delivery from the E3 region of replicating human adenovirus: evaluation of the E3B region. *Gene Ther.* 8: 1142-1148.
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REVIEWS AND BOOK CHAPTERS

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6. **Hermiston, T**. 2000. Gene delivery from replication-selective viruses; arming guided missiles in the war against cancer. *J Clin Invest* 105: 1169-1172.
7. **Hermiston, T**. 2002. Fighting fire with fire: attacking the complexity of human tumors with armed therapeutic viruses. *Curr Opin Mol Ther* 4: 334-342.
8. **Hermiston, TW**, and Kuhn, I. 2002. Armed therapeutic viruses: strategies and challenges to arming oncolytic viruses with therapeutic genes. *Cancer Gene Ther.* 9: 1022-1035.
9. **Hermiston, TW** and Kirn, DH. 2005. Genetically based therapeutics for cancer: similarities and contrasts with traditional drug discovery and development. *Mol Ther* 11: 496-507.
10. Thorne, SH, **Hermiston T**, Kirn D. 2005. Oncolytic virotherapy: approaches to tumor targeting and enhancing antitumor effects. *Semin Oncol.* 32: 537-548.
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12. Bauzon, M., **Hermiston, T**. 2008. Exploiting diversity: genetic approaches to creating highly potent and efficacious oncolytic viruses. *Curr Opin Mol Ther* 10: 350-355.

Intellectual Property – Granted Patents

- ◆ Shen, Y., Nye, J., and **Hermiston, T.** – US 6635244 – Adenovirus E1B-55K Single Amino Acid Mutants and Methods of Use
- ◆ **Hermiston, T.**, and Nye, J. - US 6764674 - Adenovirus E1B Shuttle Vectors
- ◆ Laquerre, S., and **Hermiston, T.** - US 6723316 – Herpes Simplex Virus-1 Glycoprotein C Mutants for Treating Unwanted Hyperproliferating Cell Growth
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