UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC. and
MERCK SHARP & DOHME CORP.
Petitioners

v.

GENENTECH, INC. AND CITY OF HOPE
Patent Owners

Case IPR2016-00710[1]
U.S. Patent No. 6,331,415

REBUTTAL DECLARATION OF ROGER D. KORNBERG
IN SUPPORT OF MERCK'S REPLY TO PATENT OWNERS' RESPONSE

[1] Case IPR2017-00047 has been joined with this proceeding.

TABLE OF CONTENTS

I. INTRODUCTION

I, Roger D. Kornberg, hereby declare and state as follows:

1. I have been asked by counsel for Merck Sharp & Dohme Corp. ("Merck") to provide expert opinions in the above-captioned matter in rebuttal to the expert declarations offered by John Fiddes, Ph.D. (Ex. 2019) and Reiner Gentz, Ph.D. (Ex. 2021) on behalf of Genentech, Inc. ("Genentech") and City of Hope (collectively, "Patent Owners") as well as the arguments made in the Patent Owners' Response (Paper No. 31).

2. I have prepared this declaration in connection with Petitioners' Reply concerning the unpatentability of certain claims of U.S. Patent No. 6,331,415 ("the '415 patent"), which I understand is being filed by Merck concurrently with this declaration.

3. I reserve the right to revise, supplement, and/or amend my opinions stated herein based on new information and on my continuing analysis of the materials already provided, particularly in view of any new arguments raised by Patent Owners or their experts.

4. The fact that I do not herein address all of the opinions set forth in Dr. Fiddes' declaration or Dr. Gentz's declaration does not mean that I concede or agree with them.

II. BACKGROUND AND QUALIFICATIONS

5. As further detailed in my CV, attached as Exhibit A to this declaration, I received a Bachelor of Science degree in Chemistry from Harvard University in 1967 and a Ph.D. in Chemical Physics from Stanford University in 1972. My thesis described my discovery of "flip-flop" and lateral diffusion of phospholipids in bilayer membranes.

6. I conducted postdoctoral work at the Laboratory of Molecular Biology in Cambridge, where I studied X-ray diffraction with Nobel Laureates Aaron Klug (awarded for the development of electron crystallography and studies of nucleic acid protein complexes) and Francis Crick (awarded for the discovery of the double helix structure of DNA) from 1972-1975. At Cambridge, I discovered the nucleosome, the basic protein complex responsible for packaging chromosomal DNA in the nucleus of eukaryotic cells.

7. Thereafter, I returned to the U.S. as a professor of Biological Chemistry at Harvard Medical School from 1976-1977, and then a professor of Structural Biology at Stanford University School of Medicine from 1978-2003. Since 2003, I have been the Winzer Professor in Medicine in the Department of Structural Biology at Stanford Medical School.

8. In 2006, I won the Nobel Prize in Chemistry for my research on the molecular basis of eukaryotic transcription, the process by which genetic

information from DNA is copied into RNA. I discovered the structure of RNA polymerase II, a giant multi-protein (*i.e.*, multimeric) complex. I also discovered additional multimeric complexes required for gene transcription, including the 21-protein "Mediator," which is responsible for all regulation of gene transcription.

9. My research group at Stanford continues to elucidate the fundamental basis of gene regulation by studying the molecular machines involved in transcription, reconstitution of the process with purified components, structure determination of the transcription machinery, and structure-function relationships in chromatin, the natural DNA template for transcription.

10. In addition to the Nobel Prize, I have also won over 25 other awards and honors for my research, including the Eli Lilly Award in Biological Chemistry in 1981, the Passano Award in 1982, the Harvey Prize in 1997, the Gairdner International Award in 2000, the Welch Award in Chemistry in 2001, the Grand Prize of the French Academy of Sciences in 2003, and the Horwitz Prize in 2006.

11. I have authored over 200 refereed journal articles, including 150 articles related to protein structure and folding, gene regulation, and transcription control. I have honorary degrees from universities in Europe and Israel, including the Hebrew University, where I am a Professor. I am also a Professor at Shanghai Tech University in China and Konkuk University in Korea. I have also been elected to the U.S. National Academy of Sciences, and am a member of several academic and

professional societies throughout the world, including the Royal Society, the Japanese Biochemical Society, the American Academy of Arts and Sciences, and the European Molecular Biology Organization.

12. I have also served, either currently or in the past, on scientific advisory boards and boards of directors for various companies and organizations, *e.g.*, Crystal Discovery, Inc., ChromaDex corporation, Xenetic Biosciences, Inc., OphthaliX Inc., Protalix BioTherapeutics, Inc., Oplon Ltd., Pacific Biosciences, StemRad, Ltd., OPKO Health, Inc., Epiphany Biosciences, Inc., SuperGen Inc., BioCancell Ltd., InterX Inc., Predictive Therapeutics Inc., Sensor Kinesis Corp., Cognos Corp., Aposense Inc., and Teva Pharmaceutical Industries. For several of these companies I am chief scientist, chairman of the board or executive CEO.

III. MATERIALS CONSIDERED

13. In forming the opinions set forth herein, I have considered and relied upon my education, knowledge of the relevant fields, and experience. I have also considered the materials identified in this report and those listed in Exhibit B.

14. I reserve the right to rely upon additional materials to respond to arguments raised by Patent Owners and their experts. I may also consider additional documents and information in forming any necessary opinions, including documents that may not yet have been provided to me.

IV. COMPENSATION

15. I am being compensated by Merck for my work on this case at my standard consulting rate of $25,000 per quarter. My compensation is not contingent upon the results of my analysis or the substance of my testimony. I have no stake in the outcome of this proceeding or any related litigation or administrative proceedings. I have no financial interest in Merck, and similarly have no financial interest in the '415 patent or its owner.

V. *INTER PARTES* REVIEW OF THE '415 PATENT

16. I understand that the Board has instituted the *inter partes* review of claims 1-4, 11, 12, 14, 18-20, and 33 (the "Challenged Claims") of the '415 patent on the following grounds:

- Ground 1: Whether claims 1, 3, 4, 11, 12, 14, 19, and 33 of the '415 patent are obvious over U.S. Patent No. 4,495,280 ("Bujard") (Ex. 1002) in view of Arthur D. Riggs and Keiichi Itakura, *Synthetic DNA and Medicine*, 31 AM. J. HUM. GENET., 531-538 (1979) ("Riggs & Itakura") (Ex. 1003);

- Ground 2: Whether claims 1, 2, 18, 20, and 33 of the '415 patent are obvious over the Bujard patent in view of P.J. Southern and P. Berg, *Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under Control of the SV40 Early Region Promoter*, 1 J. MOLECULAR AND APPLIED GENETICS 327-341 (1982) ("Southern") (Ex. 1004).

17. I understand that the Board previously instituted the *inter partes* review of the Challenged Claims on the same grounds in a related proceeding. (Ex. 2003,

IPR2015-01624, Paper 15). I also understand that the Board adopted the same reasoning in instituting the instant *inter partes* review.

18. I understand that Petitioners have offered the Declaration of Jefferson Foote, Ph.D. (Ex. 1006) and the Declaration of Kathryn Calame, Ph.D. (Ex. 1059) in support of their petition for *inter partes* review. The purpose of this declaration is not to supplement the opinions rendered by Dr. Foote or Dr. Calame. Rather, the scope of my opinions herein is limited to responding to certain opinions made by Dr. Fiddes and Dr. Gentz.

A. Relevant Legal Standards

19. In this section I briefly describe my understanding of certain legal standards that are relevant to my opinions in this declaration. I am not an attorney and am relying only on my understanding of these standards as they were explained to me by Merck's attorneys.

1. Legal Standard for Prior Art

20. I understand that a patent or other publication must first qualify as prior art before it can be used to invalidate a patent claim. I also understand that:

(1) a U.S. or foreign patent qualifies as prior art to an asserted patent under 35 U.S.C. § 102(a) if the date of issuance of the patent is prior to the invention of the asserted patent. I further understand that a printed publication, such as an article published in a

magazine or trade publication, qualifies as prior art under Section 102(a) to an asserted patent if the date of publication is prior to the invention of the asserted patent.

(2) a U.S. or foreign patent qualifies as prior art to an asserted patent under 35 U.S.C. § 102(b) if the date of issuance of the patent is more than one year before the filing date of the asserted patent. I further understand that a printed publication, such as an article published in a magazine or trade publication, constitutes prior art under 102(b) to an asserted patent if the publication occurs more than one year before the filing date of the asserted patent.

(3) a U.S. patent qualifies as prior art to an asserted patent under 35 U.S.C. § 102(e) if the application for that patent was filed in the United States before the invention of the asserted patent claim.

21. I understand that in an *inter partes* review proceeding, invalidity must be shown by a preponderance of the evidence.

2. Legal Standard for Obviousness

22. I understand that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the challenged claims, (3) the level of

ordinary skill in the pertinent art, and (4) the existence of secondary considerations such as commercial success, long-felt but unresolved needs, failure of others, etc.

23. I understand that an obviousness evaluation can be based on a combination of multiple prior art references. I am informed by counsel that the prior art references themselves may provide a suggestion, motivation, or reason to combine, but at other times the nexus linking two or more prior art references is simple common sense. I am further informed by counsel that obviousness analysis recognizes that market demand often drives innovation, and that a motivation to combine references may be supplied by the direction of the marketplace.

24. I understand that a person of ordinary skill in the art provides a reference point from which the prior art and claimed invention should be viewed. I am informed by counsel that obviousness cannot be based on the hindsight combination of components selectively drawn from the prior art.

25. I understand that if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

26. I understand that practical and common sense considerations should guide a proper obviousness analysis because familiar items may have obvious uses beyond their primary purposes. I am further informed by counsel that a person of

ordinary skill in the art looking to overcome a problem will often be able to fit the teachings of multiple publications together like pieces of a puzzle, although the prior art need not be like two puzzle pieces that must fit perfectly together. I am informed by counsel that obviousness analysis therefore takes into account the inferences and creative steps that a person of ordinary skill in the art would employ under the circumstances.

27. I understand that a particular combination may be proven obvious merely by showing that it was obvious to try the combination. For example, when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp because the result is likely the product not of innovation but of ordinary skill and common sense. I am informed by counsel that the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, obviousness likely bars its patentability.

28. I understand that a proper obviousness analysis focuses on what was known or obvious to a person of ordinary skill in the art, not just the patentee.

Accordingly, I am informed by counsel that any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

29. I understand that a claim can be obvious in light of a single reference, without the need to combine references, if the elements of the claim that are not found explicitly or inherently in the reference can be supplied by the common sense of one of skill in the art.

30. I understand that a person of ordinary skill could have combined two pieces of prior art or substituted one prior art element for another if the substitution can be made with predictable results, even if the swapped-in element is different from the swapped-out element. In other words, the prior art need not be like two puzzle pieces that must fit together perfectly. The relevant question is whether prior art techniques are interoperable with respect to one another, such that that a person of skill would view them as a design choice, or whether a person of skill could apply prior art techniques into a new combined system.

31. I understand person of ordinary skill must be motivated to combine the two pieces of prior art and have a reasonable expectation of success. With respect to the motivation to combine, I understand that to combine references may come from the references themselves, from the knowledge of those skilled in the art, or from the very nature of the problem sought to solved that would lead inventors to

look to references relating to possible solutions to that problem. I further understand that the motivation need not be expressly stated, but can be inferred.

32. With respect to a respect to a reasonable expectation of success, I understand that refers to the likelihood of success in combining references to meet the limitations of the claimed invention. I have been informed that evaluating whether there is a reasonable expectation of success, there is no requirement for absolute predictability of success—all that is required is a reasonable expectation of success. I understand that where the reference discloses or suggests using its teachings toward the direction of the challenged patent, this is strong evidence for a reasonable expectation of success.

33. I understand that secondary indicia of non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success or lack of commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) taking of licenses under the patent by others; and (6) deliberate copying of the invention. I am also informed by counsel that there must be a causal relationship between any such secondary indicia and the invention. I am further informed by counsel that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

34. Finally, I understand that the legal question of obviousness is resolved on the basis of underlying factual determinations, as described above, which differ from a non-statutory "obviousness-type double patenting" determination, which I have been informed came up in proceedings before the PTO.

B. Level of Ordinary Skill in the Art

35. I understand that factors relevant to the level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field. I also understand these factors are not exhaustive but are merely a guide to formulating a definition of a person of ordinary skill in the art ("person of ordinary skill").

36. I understand that Drs. Foote and Calame have previously opined that a person of ordinary skill would have a Ph.D. in molecular biology (or a related discipline, such as biochemistry) with at least 1-2 years of postdoctoral experience, or an equivalent amount of combined education and laboratory experience. The person of ordinary skill would also have experience using recombinant DNA techniques to express proteins and have some familiarity with protein chemistry, immunology, and antibody production, structure, and function. I have applied this definition in forming the opinion expressed herein.

37. I understand that Patent Owners do not dispute this definition of a person of ordinary skill in the art. (Paper 31, Patent Owners' Response at 23).

38. My opinions are from the point of view of this person of ordinary skill working in the field of heterologous, *i.e.*, recombinant, protein expression as of April 1983. Generally, and as used herein, a heterologous protein is one that is foreign to a host cell and is introduced using recombinant DNA techniques. For convenience, the produced proteins are sometimes called recombinant proteins, but technically it is the genes that are recombinant, rather than the protein itself.

39. I understand that Dr. Fiddes has his own articulation of the level of skill in the art. (Ex. 2019, Fiddes Decl. ¶¶ 147-49). I do not believe Dr. Fiddes' definition is materially different from my own, and my opinions in this declaration apply equally under either articulation of the level of skill in the art.[2]

C. Claim Construction

---

[2] Dr. Gentz does not define the level of skill in the art. To the extent that his references to "a scientist with a Ph.D. in molecular biology or a related discipline," (*see, e.g.*, Ex. 2021, Gentz Decl. ¶¶ 30, 36), constitute his articulation of the level of skill in the art, I do not believe that definition is materially different from my own, and my opinions in this declaration apply equally under either articulation of the level of skill in the art.

40. In responding to Dr. Fiddes and Dr. Gentz below, I have interpreted the Challenged Claims under the "broadest reasonable interpretation" of the claims "consistent with the specification," and have read the claim language in light of the specification as it would be understood by a person of ordinary skill, which I understand is the approach taken by the Patent Trial and Appeal Board of the PTO in an *inter partes* review.

VI. SUMMARY OF OPINIONS

41. I have been asked to provide my expert opinion in response to certain opinions offered by Dr. Fiddes and Dr. Gentz concerning the state of the art in April 1983, the Bujard patent, Riggs & Itakura, and Southern.

42. Dr. Fiddes' and Dr. Gentz's opinions are based on an overly narrow and selective reading of the Bujard patent. It is my opinion that Bujard (i) teaches the use of the co-expression of multiple, distinct eukaryotic genes of interest in a single host cell, (ii) suggests a method for producing antibodies, and (iii) suggests the *in vivo* assembly of a multimeric protein encoded by more than one gene in a single host cell. For a person of ordinary skill, the obvious import of applying the teachings of Bujard to produce the claimed subject matter would have been reinforced by the contemporaneous market demand to produce antibodies recombinantly.

43. In addition, I disagree with Dr. Fiddes' and Dr. Gentz's opinions regarding the scope and teachings of Riggs & Itakura and Southern, alone and in

combination with Bujard. In my opinion, there was a strong motivation to combine Bujard with either Riggs & Itakura or Southern.

44. It is my opinion that a person of ordinary skill would have been motivated to apply the teachings of either Riggs & Itakura or Southern with Bujard to appreciate the feasibility of the co-expression of multiple independent proteins of interest in a single eukaryotic cell to make antibodies. First of all, contrary to Dr. Fiddes' opinions, Bujard explicitly teaches that antibodies can be made by its method. Thus, when Riggs & Itakura disclosed the *in vitro* assembly of two chains and expressly noted the application of such technique to antibody production, it is obvious that such teachings will likewise extend to the explicit teachings of antibody production referenced in Bujard. Moreover, I disagree with Dr. Fiddes' characterization of Southern. Southern's teaching of double transfection to produce two or more proteins is likewise equally applicable to, and would be read by a person of ordinary skill to include, the production of antibodies as taught in Bujard.

45. In my opinion, a person of ordinary skill would have recognized that expressing two proteins of interest could have been accomplished by assembling the proteins *in vitro* as taught by Riggs & Itakura or, when the two genes are co-transformed in the cell by separate vectors, to provide for separate expression of the multiple desired proteins of interest, as taught by Southern. A person of ordinary skill would have a reasonable expectation of success to use the two different vectors

disclosed in Southern to co-transform a mammalian host cell with multiple, different genes of interest to separately express complex, eukaryotic proteins in a single host cell. Similarly, a person of ordinary skill would have been equally motivated to use these same teachings to co-transform a single host cell with one vector to separately express multiple, different proteins of interest.

46. In my opinion, a person of ordinary skill would have been motivated to use the tools taught by Bujard to make antibodies using any of the above teachings relating to the co-transformation of recombinant DNA molecules and co-expression techniques (*e.g.*, as taught in Bujard, Riggs & Itakura, or Southern) with a reasonable expectation of success in achieving the subject matter of the Challenged Claims.

47. It is further my opinion that (i) the combination of Riggs & Itakura and Bujard renders the Challenged Claims of the '415 patent obvious, and (ii) the combination of Southern and Bujard renders the Challenged Claims of the '415 patent obvious.

VII. THE CHALLENGED CLAIMS

48. I have reviewed Dr. Foote's description of the Challenged Claims and his overview of the '415 patent and have applied that description in forming the opinions expressed herein. (Ex. 1006, Foote Decl. ¶¶ 26-41).

VIII. THE STATE OF THE ART FOR RECOMBINANT PROTEIN PRODUCTION IN APRIL 1983

49. I understand that Patent Owners and Dr. Fiddes have suggested that there was a prevailing mindset in the early 1980s that only one protein of interest should be made recombinantly in a single host cell. (*See, e.g.*, Paper 31, Patent Owners' Response at 10-13; Ex. 2019, Fiddes Decl. ¶¶ 87, 96). I disagree. I was active in the field in the early 1980s and I held no such view; nor did any other scientist I know subscribe to such a view. In fact, even in the early 1980s, scientists possessed the ability to introduce multiple genes into single host cells for the purpose of recombinant expression of multiple proteins. At that time, recombinant DNA was becoming a tool of virtually every laboratory in any field of biology or biochemistry. Many recombinant DNA techniques had already become standard practice and scientists understood the practical impact and benefits of being able to manipulate genes and engineer proteins of interest in a single host cell rather than having to employ multiple expression systems across multiple host cells. The materials and methods for doing so had developed in a step-wise fashion, and all of the steps had been accomplished and disclosed prior to April 1983.

50. Dr. Fiddes acknowledges that "recombinant gene expression technology was seen as a promising way to produce proteins of interest" in April 1983, but claims that "many of the biological mechanisms controlling the expression of foreign DNA and the assembly of the resulting proteins were still poorly

understood at the time." (Ex. 2019, Fiddes Decl. ¶ 57). I disagree. I was personally familiar with the materials and methods used to recombinantly-produce proteins in April 1983. As of that date, I was a professor of Structural Biology at Stanford University School of Medicine. Both myself and the researchers in my lab had been using recombinant DNA techniques to manipulate and produce a wide variety of proteins for years. Indeed, numerous references describe the widespread use and application of these techniques and protocols for cloning genes, transforming host cells and analyzing recombinant protein expression. (*See, e.g.,* Ex. 1095, Maniatis, T., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory (1982)). In the 1970s, recombinant DNA techniques were being used to produce proteins by transfecting cells with DNA sequences not already present in those cells, and then propagating the cells containing the heterologous DNA *in vitro* under conditions that cause the cell to produce the protein coded by that DNA. One notable example is the work of Stanley Cohen and Herbert Boyer, two researchers who shared the Albert Lasker Basic Medical Research Award with my Stanford University School of Medicine colleagues, Paul Berg (co-author of Southern, Ex. 1004) and Dale Kaiser, for recombinantly expressing heterologous proteins in cells. Their work involved co-transfecting a vector with DNA foreign to that host cell (*e.g.,* DNA coding for eukaryotic proteins in a prokaryotic cell) and selecting for the cells that were successfully co-transfected or co-transformed and have a certain

"phenotypic property" by virtue of co-expressing a marker protein recombinantly. Thus, the cells are grown in conditions such that only cells that have acquired the selectable marker survive. The Cohen & Boyer technique, documented in U.S. Patent No. 4,237,224 (Ex. 1005), has been used extensively over the last forty plus years and remains a common method of expressing eukaryotic proteins in bacterial cells.

51. Dr. Fiddes also opines that "[a]s of April 1983, *E. coli*, a prokaryotic bacterial organism, was the best characterized and most widely used host cell for recombinantly expressing protein," and that "a scientist working in the field would have understood that the production of even a simple monomeric protein in a single cell system was a challenging undertaking." (Ex. 2019, Fiddes Decl. ¶¶ 58, 73-74). Dr. Fiddes also claims that a person of skill in the art interested in recombinant expression in eukaryotic cells would only have taken guidance from prior experience in eukaryotic cells, and not prokaryotic host cells. (Ex. 1113, Fiddes Dep. Tr. at 231:24-232:17). I disagree with this opinion. While much of the original recombinant DNA work was conducted in prokaryotic host cells, and most typically the bacterium *E. coli,* there was a general recognition in the field that producing eukaryotic proteins recombinantly in their "natural" environment of a single eukaryotic host cell was desirable, for several reasons. For one, prokaryotic host cells lack the cellular machinery of a eukaryotic cell to naturally process (*e.g.*,

phosphorylate and glycosylate) a eukaryotic protein once it is expressed. Likewise, it had been shown that prokaryotic host cells had posed difficulties such as unworkably low or non-existent recombinant protein production, and purifying eukaryotic proteins free of bacterial endotoxins. In response to this need to overcome the disadvantages of prokaryotic host cells, advances were soon made and the tools developed to manipulate eukaryotic proteins, through similar cloning, transformation, expression and recovery techniques, in eukaryotic host cells. In a relatively rapid timeframe (a matter of a few years, around the late 1970s), different groups of researchers on the East and West Coasts developed technologies that could be used as a platform to express eukaryotic genes in eukaryotic host cells. With these tools in hand, using a eukaryotic cell as a host was a practical means by which to produce eukaryotic proteins.

52. Dr. Fiddes further opines that "there were challenges in trying to recombinantly express a eukaryotic protein in a prokaryotic host cell," and that "recombinant protein expression in eukaryotic host cells was also in its infancy in April 1983." (Ex. 2019, Fiddes Decl. ¶¶ 58, 71). I disagree with Dr. Fiddes. At the time, a group of researchers on the East Coast developed a co-transformation technique that is often referred to as the Wigler Method. Dr. Michael Wigler and his colleagues demonstrated the ability to introduce and express exogenous genes in eukaryotic host cells. Similar to the Cohen and Boyer prokaryotic approach, Dr.

Wigler co-transformed DNA encoding a selectable marker along with DNA encoding one or more proteins of interest, thereby allowing selection of host cells that have been successfully transformed. Dr. Wigler solved the problems resulting from the expression of eukaryotic proteins in a prokaryotic host cell by designing a eukaryotic expression system that could integrate into the chromosome of the eukaryotic host cell and create amplified expression of multiple different recombinant proteins of interest in a single eukaryotic cell. Dr. Wigler's research appeared in a series of high-profile publications, (*e.g.*, Ex. 1096, Wigler M., et al., *Transfer of Purified Herpes Virus Thymidine Kinase Gene to Cultured Mouse Cells*, Cell 11(1):223-32 (1977); Ex. 1097, Wigler M. et al., *Transformation of Mammalian Cells with Genes from Procaryotes and Eucaryotes*, Cell 16(4):777-85 (1979)), and is also the subject of U.S. Patent No. 4,399,216 (Ex. 1018), on which he is a co-inventor.

53. In support of his opinion that recombinant protein expression in eukaryotic cells was subject to uncertainty and problems, Dr. Fiddes states that "no multimeric protein with different polypeptide chains had been produced in a eukaryotic host cell via expression of all the constituent parts of the protein from exogenous genes." (Ex. 2019, Fiddes Decl. ¶ 71). As a result, according to Dr. Fiddes, "there was no 'cookie-cutter' approach that ensured success to recombinantly expressing a eukaryotic protein." (*Id.* ¶ 73). I disagree with Dr.

Fiddes. The eukaryotic expression vector taught by Wigler and his colleagues was a powerful tool, and it was both designed for and quickly adopted for easy use in certain eukaryotic cell types. The West Coast researchers affiliated with Prof. Berg expanded these teachings through the development of a new eukaryotic expression vector—the pSV2 vector—that could be used in a wider range of eukaryotic host cells for the same purpose—to allow multiple genes of interest to be co-transformed and their proteins co-expressed and produced in a single eukaryotic host cell. Indeed, I recall when Paul Berg was awarded the Nobel Prize in Chemistry in 1980 for his work on recombinant DNA technology, and I personally applied his teachings in my research.[3] The work describing the Berg lab's development of vectors suitable for co-transformation and co-express of eukaryotic proteins in eukaryotic host cells is described in a series of publications, culminating in Southern (Ex. 1004). As detailed further below, this important work was both well accepted in the scientific community and its significance appreciated.

---

[3] Indeed, I have known Paul Berg since childhood and I worked in his biochemistry laboratory in the 1960s. Moreover, Paul Berg was a postdoctoral fellow in the laboratory of my father, Arthur Kornberg, and faculty member in my father's department (of biochemistry, at Stanford University School of Medicine) for his entire career.

54. In my opinion, Dr. Fiddes mischaracterizes the state of the art when he opines that "there was no 'cookie-cutter' approach that ensured success to recombinantly expressing a eukaryotic protein." (Ex. 2019, Fiddes Decl. ¶ 73). To the contrary, persons of ordinary skill had at their disposal the tools to move forward easily and produce a wide variety of complex eukaryotic proteins, using a single eukaryotic cell as a host, with reasonable predictability. Importantly, each of these steps had been realized as separately providing and collectively refining the means by which persons of ordinary skill could express multiple eukaryotic proteins of interest in a single host cell, all prior to the filing of the '415 patent.

55. I understand that Patent Owners and Dr. Fiddes have suggested that a person of ordinary skill in the art would not have been motivated to combine Bujard with either Riggs & Itakura or Southern. (*See, e.g.*, *id.* ¶¶ 246, 306; Paper 31, Patent Owners' Response at 43-44, 55-56). I disagree. In addition to the specific reasons set forth further below, it is my opinion that a person of ordinary skill in the art would have been motivated to combine Bujard and either Riggs & Itakura or Southern, as each of the references are from the exact same field: use of recombinant DNA technology as a means to produce eukaryotic proteins.

56. Notably, in claiming that a skilled artisan would not have been motivated to combine Bujard with either Riggs & Itakura or Southern, Dr. Fiddes overlooks the significant contemporaneous market demand to produce antibodies

recombinantly. In the late 1970s and early 1980s, the scientific community recognized the power and ability of recombinant DNA technology to produce therapeutic proteins, including antibodies. (*See, e.g.*, Ex. 1098, Miller, W., *Use of Recombinant DNA Technology for the Production of Polypeptides*, Adv. Exp. Med. Biol., 118:153-174 (1979) at 169 (discussing the use of recombinant DNA for the production of therapeutics, stating, *e.g.*: "… it appears the era of recombinant DNA pharmaceuticals is immediately imminent. Virtually any polypeptide could, in theory, be produced on an industrial scale in this fashion: immunoglobulins, ...")). This demand would have further fueled the person of ordinary skill's desire and motivation to combine the above references so as to satisfy the need and follow the direction of the marketplace to produce therapeutically-desirable human antibodies.

57. Dr. Fiddes opines that the prevailing mindset in April 1983 would have concerned a "one-polypeptide-per-host-cell approach," which was used for the synthesis of insulin. (*See, e.g.*, Ex. 2019, Fiddes Decl. ¶¶ 87, 97). I disagree with Dr. Fiddes. Dr. Fiddes' opinions on the "prevailing mindset" of constructing one-recombinant-protein-per-cell do not accurately reflect the thinking of a person of ordinary skill in April 1983. Numerous scientific publications and presentations taught co-expressing more than one "protein of interest" in a single host cell and, by 1983, vectors had been designed with the specific goal of enabling the encoding of multiple genes of interest on a single vector for co-expression of several genes of

interest in a single host cell. (*See, e.g.*, Ex. 1069, Berg, P., *Dissections and Reconstructions of Genes and Chromosomes*, Science, 213:296-303 (1981); Ex. 1120, Mulligan, R.C., & Berg, P., *Expression of a Bacterial Gene in Mammalian Cells*, Science 209: 1422-1427 (1980)).

58. Dr. Fiddes also states that, because "the recombinant expression of even a simple eukaryotic protein raised numerous uncertainties," it was not clear whether "it was even possible" to "recombinantly express an antibody." (Ex. 2019, Fiddes Decl. ¶ 101). Dr. Fiddes states that "as of the early 1980s, scientists had just started to consider whether antibody production could be accomplished using recombinant techniques, and [ ] any possibility of doing so was something far off in the future (if at all)." (*Id.* ¶ 104). I disagree with Dr. Fiddes. A person of ordinary skill would have recognized that a multimeric protein, such as an antibody, is particularly well-suited for expression in a single host cell using the techniques taught by the Berg lab. Researchers knew from the earliest days of recombinant DNA technology that using a single host cell to express multiple genes of interest has a number of advantages over using multiple host cells. Using only one host cell mimics the way multimeric proteins are synthesized naturally and is more efficient than using multiple host cells.

59. I also understand that Dr. Fiddes contends that research regarding antibodies and recombinant gene expression between May 1981 and April 1983

confirmed that there was uncertainty and unpredictability as to whether antibodies could be produced recombinantly. (*Id.* at 41). According to Dr. Fiddes, the research at that time "would have suggested to a person of ordinary skill in the art that taking even the incremental step of expressing a single immunoglobulin chain in a single host presented problems and challenges that remained unsolved in April 1983." (*Id.* ¶ 109). Rather, Dr. Fiddes opines that "in 1982, scientists were still identifying the factors involved in the production of even a single antibody light chain recombinantly (and [ ] no one had reported success producing the more complex heavy chain)." (*Id.* ¶ 112).

60. I disagree with Dr. Fiddes. Dr. Fiddes specifically points to the work of Rice & Baltimore (Ex. 1020) as an example. In particular, Dr. Fiddes focuses on the statement in Rice & Baltimore that "[a]lthough much is now known about the Ig gene structure, relatively little is known about the molecular mechanism that control Ig gene expression." (Ex. 2019, Fiddes Decl. ¶ 114 (quoting Ex. 1020, at 7862)). From this statement, Dr. Fiddes concludes that "Rice & Baltimore did not indicate that the authors ever considered producing functional immunoglobulins by transfecting individual host cells with both heavy and light chain genes." (Ex. 2019, Fiddes Decl. ¶ 114). I disagree with Dr. Fiddes. To be clear, Rice & Baltimore used a vector (the pSV2-neo vector) to recombinantly express an immunoglobulin light chain, which Dr. Fiddes concedes. (Ex. 2019, Fiddes Decl. ¶ 113; Ex. 1113, Fiddes

Dep. Tr. at 257:18-258:2). And Rice & Baltimore specifically stated that "[t]he possibility that transcription of the light chain gene is controlled by a product of the heavy chain locus is an interesting possibility and needs further investigation." (Ex. 1020, at 7865). In other words, Rice & Baltimore were interested in whether it was possible to place both the heavy and light chains on the same vector. Thus, I think it is misleading for Dr. Fiddes to state that Rice & Baltimore—let alone a person of ordinary skill in the art at the time—never "considered producing functional immunoglobulins by transfecting individual host cells with both heavy and light chain genes." (Ex. 2019, Fiddes Decl. ¶ 114).

61. Dr. Fiddes also cites the work of Vernon Oi and Sherie Morrison (Ex. 1031) as another example. (*Id.* ¶¶ 115-16). I disagree with Dr. Fiddes' mischaracterization of the Oi reference. Oi also "obtained expression of the light chain in two cell lines." (*Id.* ¶ 115). However, again focusing on the shortcomings, Dr. Fiddes states that "two other host cells failed to produce any detectable amounts of light chain after transfection." (*Id.*). The authors found the lack of expression "surprising" because one of the cell lines had previously been successful. (*Id.*). According to Dr. Fiddes, the authors' "surpris[e]" demonstrates that they viewed the expression of "even a single antibody light chain as an uncertain and unpredictable endeavor with no reasonable expectation of success." (*Id.*). Oi actually demonstrates the opposite. As Dr. Fiddes acknowledges, Oi successfully

demonstrated the expression of the light chain in two cell lines, which alone undermines Dr. Fiddes' assertion that there was "no reasonable expectation of success." (*Id.* ¶ 116; Ex. 1113, Fiddes Dep. Tr. at 108:7-22). Moreover, against the backdrop of the successful expression, the authors' "surpris[e]" at the unsuccessful cell lines actually demonstrates that they were *expecting* the lines to successfully express the light chain, again undermining Dr. Fiddes' speculation that there was "no reasonable expectation of success." (Ex. 2019, Fiddes Decl. ¶ 116). And, as Dr. Fiddes concedes, Oi highlighted for a person of skill in the art that promoters were important to achieving the right translation and cell production. (Ex. 1113, Fiddes Dep. Tr. at 115:20-117:11).

62. Dr. Fiddes also references the work of Ochi (Ex. 1021, "Ochi I"), which Dr. Fiddes states "confirms the overall uncertainty and unpredictability in the field." (Ex. 2019, Fiddes Decl. ¶¶ 117-19). Dr. Fiddes misconstrues Ochi. As Dr. Fiddes notes, Ochi successfully transformed four cell lines that showed detectable antibody production, but ten others did not show detectable antibody production. Importantly, Dr. Fiddes concedes that Ochi was able to recombinantly express antibodies despite the purported uncertainty in the field. (Ex. 1113, Fiddes Dep. Tr. at 257:18-258:2). In using Ochi to show the supposed uncertainty and unpredictability in the field, Dr. Fiddes focuses on Ochi's statement that the "mechanisms responsible for the regulation of the expression of rearranged immunoglobulin genes are poorly

understood." (Ex. 2019, Fiddes Decl. ¶ 119 (quoting Ex. 1021, at Abstract)). However, as this statement makes clear, the issue was the *regulation* of expression, not the method. And, as Dr. Fiddes admits, it would not be surprising to a person of skill in the art that the variability of gene expression might turn on whether the regulatory elements of the gene are present or functioning. (Ex. 1113, Fiddes Dep. Tr. at 147:2-6). Moreover, Ochi goes on to explain that "[e]xperiments are in progress to determine the molecular basis for the difference in the *level of expression* of the κ_{TNP} gene in the various transformants." (Ex. 1021, at 342 (emphasis added)). Again, as this statement makes clear, the issue was one of yield, not the expression methodology. Accordingly, I disagree with Dr. Fiddes' assertion that Ochi demonstrates the supposed "uncertain and unpredictable state of art." (Ex. 2019, Fiddes Decl. ¶ 119).

63. I also understand that Owners have argued that the size and complexity of an antibody—a tetramer of approximately 150,000 Daltons—means that a person of ordinary skill would not have had a reasonable expectation of successfully expressing the heavy and light chains in a single host cell. (*See, e.g., id.* ¶¶ 43-44, 79, 266). This argument lacks merit. Contrary to Patent Owners' statement, it was widely assumed in April 1983 that virtually any protein—no matter how large or complex—could be expressed using recombinant DNA technology. In fact, proteins larger than immunoglobulins had already been successfully expressed using

recombinant DNA techniques. (*See, e.g.*, Ex. 1072, Pauza, C. D. et al., *Genes Encoding Escherichia coli Aspartate Transcarbamoylase: The pyrB-pyrI Operon*, Proc. Natl. Acad. Sci. USA, 79:4020-4024 (July 1982); Ex. 1073, Wild, J. et al., *A Mutation in the Catalytic Cistron of Aspartate Carbamoyltransferase Affecting Catalysis, Regulatory Response and Holoenzyme Assembly*, Nature 292:373-375 (July 23, 1981); Ex. 1075, Roof, W. et al., *The Organization and Regulation of the pyrBI Operon in E. coli Includes a Rho-Independent Attenuator Sequence*, Mol Gen Genet 187:391-400 (1982); Ex. 1099, Turnbough, C. et al., *Attenuation Control of pyrBI Operon Expression in Escherichia coli K-12*, Proc. Natl. Acad. Sci. USA, 80:368-372 (January 1983); Ex. 1076, Navre, M. & Schachman, H.K., *Synthesis of Aspartate Transcarbamoylase in Escherichia coli: Transcriptional Regulation of the pyrB-pyrI Operon*, Proc. Natl. Acad. Sci. USA, 80:1207-1211 (1983)). I thus disagree with Dr. Fiddes' assertion that "work with larger proteins encoded by longer stretches of DNA and mRNA would have been viewed as much more unpredictable as compared to work with shorter genes and smaller proteins." (Ex. 2019, Fiddes Decl. ¶ 79). Moreover, several of these groups reported co-expression of multiple protein chains from a one vector construct. In particular, at least three different groups used the pBR322 plasmid—the same plasmid used in the '415 patent for transforming *E. coli* cells—in the recombinant expression of multimeric proteins

before April 7, 1983.[4] (*See, e.g.*, Ex. 1073, Wild; Ex. 1075, Roof; Ex. 1099, Turnbough). Thus, it is entirely reasonable, based on this contemporaneous evidence of record, for a person of ordinary skill in April 1983 not to have been deterred by the alleged size and complexity of the immunoglobulin molecule and would have been motivated to apply the known art to target antibodies for recombinant production. I therefore disagree with Dr. Fiddes' contention that "there were no known guideposts showing recombinant expression of two genes of interest in a host cell." (Ex. 2019, Fiddes Decl. ¶ 137).

64. Finally, I also understand Dr. Fiddes and Dr. Gentz to imply that a person of ordinary skill might not have referenced patents in his or her research. (*See, e.g.*, Ex. 2019, Fiddes Decl. ¶ 96; Ex. 2021, Gentz Decl. ¶ 36). I disagree. In my opinion, a person of ordinary skill in the art would reference relevant patents, and I would charge such a person with knowledge of such patents in assessing the level of skill in the art. Dr. Fiddes appeared to concede that he is in agreement during his deposition. (*See* Ex. 1116, IPR2015-01624, Fiddes Dep. at 60:8-13).

[4] Dr. Fiddes admitted that he did not review the Wild (Ex. 1073) publication, and had not reviewed the Roof (Ex. 1075) publication in "a long time." (Ex. 1113, Fiddes Dep. Tr. at 235:10-13, 241:15-17).

65. Relatedly, I also understand that Dr. Gentz renders various opinions concerning his personal recollection from 1980-1981 and his speculation as to the knowledge and intentions of his fellow researchers during this time. (*See, e.g.*, Ex. 2021, Gentz Decl. ¶¶ 24, 26-27). While I respect Dr. Gentz's research, I understand that Dr. Gentz's involvement with the Bujard lab ceased in 1981, (*see id.* ¶ 11), whereas the relevant timeframe for assessing Bujard's teachings is April 7, 1983. Accordingly, I do not find Dr. Gentz's opinions premised in his own involvement years before the April 1983 probative of the level of skill in the art.

IX. PATENT OWNERS' AND THEIR EXPERTS' READING OF BUJARD IS OVERLY NARROW AND FAILS TO APPRECIATE THE FULL TEACHINGS OF BUJARD

66. I disagree with Dr. Fiddes and Dr. Gentz's narrow and selective reading of the Bujard teachings. Dr. Fiddes and Dr. Gentz minimize, overlook, or attempt to explain away the express teachings of Bujard. Among other things, Dr. Fiddes and Dr. Gentz opine that Bujard does not suggest co-expression of multiple distinct genes in a single host cell, does not suggest a method for producing antibodies, and does not suggest the *in vivo* assembly of a multimeric protein encoded by more than one gene. I disagree with this interpretation of Bujard, which I find to be overly narrow and untethered from the express language of Bujard. In my opinion, Bujard is clear: it teaches a method for producing proteins of interest in a transformed host cell using a plasmid vector that is optimized to

increase the efficiency of expression. (*See, e.g.*, Ex. 1002, 6:53-7:20). Bujard specifically identifies antibodies as proteins of interest. (*Id.* at 5:11-27).

67. Dr. Fiddes disagrees with the Board's finding that "Bujard relates to a process for producing polypeptides in a transformed host cell using a plasmid vector." (Paper 13, Institution Decision at 9-10; Ex. 2019, Fiddes Decl. ¶¶ 173, 211-12, 235; Ex. 2003, IPR2015-01624, Paper 15 at 11). I agree with the Board's interpretation and, as set forth more fully below, I do not believe that a person of ordinary skill would find merit to Dr. Fiddes' contentions. In my opinion, a person of ordinary skill would find the Board's reasoning to be sound and consistent with the express language of Bujard and the state of the art in 1983.

68. In my opinion, Dr. Fiddes improperly requires that Bujard disclose the purported invention of the '415 patent. That is not in dispute—the instituted grounds relate to obviousness, not anticipation. Specifically, Dr. Fiddes points out that Bujard "was filed in May 1981 – just two months after the publication of Dr. Milstein's comments," and that "an ordinarily-skilled scientist would not conclude that Bujard had solved the many problems with recombinant antibody production that Dr. Milstein had identified around the same time, including Dr. Milstein's observation that antibody production might not be possible at all." (Ex. 2019, Fiddes Decl. ¶ 107). As I understand the scope of this *inter partes* review, the question is not whether Bujard achieved the full scope of the purported invention

described in the '415 patent, but rather whether the Challenged Claims were obvious in light of Bujard *and* either Riggs & Itakura (Ex. 1003) or Southern (Ex. 1004) in April 1983—not 1981 when Bujard was filed.

69. Dr. Gentz purports to rely on his experiences in Dr. Bujard's lab from 1980-1981, at least in part as a basis for his opinion on the proper scope of Bujard. (*See* Ex. 2021, Gentz Decl. ¶¶ 11-18). However, Dr. Gentz neglects to mention his lack of involvement with the Bujard patent. In fact, while in the Bujard laboratory he had never seen a draft of the patent application, was never consulted regarding it, and did not contribute any text to it. (Ex. 1115, IPR2015-01624, Gentz Dep. at 88:10-89:24). And Dr. Gentz admits that he does not know anything about the communications between the Bujard inventors regarding the preparation of the Bujard patent application. (*Id.* at 90:1-5). Nor does Dr. Gentz know who from Dr. Bujard's or Dr. Cohen's lab was involved in preparing the application, or, importantly, what the Bujard inventors were contemplating with respect to the promoters and co-expression of different eukaryotic genes because he was not a party to their discussions. (*Id.* at 90:10-13, 116:11-17).

A. Dr. Fiddes and Dr. Gentz Adopt An Unreasonably Narrow View of Bujard

70. I disagree with Dr. Fiddes' and Dr. Gentz's overly narrow reading of the teachings of Bujard. Dr. Fiddes opines that "the focus of Bujard is different" and that Bujard simply provides "a research tool for stably cloning strong

promoters into plasmids, for use in subsequent experiments." (Ex. 2019, Fiddes Decl. ¶¶ 157, 161, 243). Similarly, Dr. Gentz states that the Bujard lab "was not focused on methods of protein production," but rather was conducting "exploratory research directed to characterizing various promoters and understanding why some are more efficient than others." (Ex. 2021, Gentz Decl. ¶ 23).

71. In my opinion, Dr. Fiddes and Dr. Gentz improperly limit Bujard to methods to screen promoters and terminators that can be cloned into plasmids for subsequent use. Patent Owners conclude that "a skilled artisan attempting to produce antibodies recombinantly would not have even considered Bujard—which does not contain *any* disclosure specific to antibody production." (Paper 31, Patent Owners' Response at 25). Dr. Fiddes renders an opinion, seeking to contrast the supposedly narrow scope of Bujard with the '415 patent:

> While Bujard teaches methods to screen for useful promoter and terminator pairs that can be cloned into plasmids for subsequent use, I do not read anything in Bujard that would have suggested to a person of ordinary skill in the art as of April 1983 constructs involving the use of multiple eukaryotic genes of interest in a single plasmid, using a balanced promoter/terminator pair as contemplated by Bujard or otherwise.

(Ex. 2019, Fiddes Decl. ¶ 169). In my opinion, Dr. Fiddes' and Dr. Gentz's positions are premised unreasonably narrow view of Bujard.

72. Bujard is directed to vectors for expressing proteins of interest in transformed host cells. Dr. Fiddes does not dispute the "fundamental" role that

vectors play in recombinant gene expression, including in the '415 patent. (*Id.* ¶¶ 52-53). As Dr. Fiddes explains, the general process of the '415 patent involves the insertion of a vector encoding for a particular gene or genes of interest into a host cell, which then expresses the gene of interest. (*Id.*). Moreover, as Dr. Fiddes states, in addition to the particular gene or genes of interest, such vector "also includes regulatory sequences such as promoters and terminators to signal the initiation and termination of transcription." (*Id.* ¶ 54). In this regard, Bujard describes a vector with four independently replaceable segments—including promoters and terminators—that is used to transform a host cell with the goal of optimizing the production of recombinant proteins encoded by the DNA sequence of interest. (Ex. 1002, 2:3-20, 3:4-62, 6:34-37, 6:53-7:20). Notably, Bujard provides methods and compositions for preparing and cloning promoters and terminators, and utilizing the strong regulatory sequences in the transcription and expression of a gene or genes of interest. (*Id.* at 2:28-32). In fact, Dr. Fiddes admits that Bujard is not simply a "research tool" but rather discusses a wide range of structural genes of interest that could be of use. (Ex. 1113, Fiddes Dep. Tr. at 187:7-20, 190:1-6).

73. Dr. Fiddes and Dr. Gentz overlook and omit the very first sentence of Bujard's "Background of the Invention" section, which acknowledges that others had already "established the feasibility of producing a wide variety of naturally

occurring and synthetic polypeptides by means of hybrid DNA technology," but that there were "continuing and extensive efforts to provide for more efficient and economic methods for producing the polypeptides." (Ex. 1002, 1:13-18). This statement makes clear Bujard's role in recombinant protein production. Moreover, Bujard further explains that "[i]t is therefore desirable that methods be provided which would allow for the screening of strong promoters and terminators and their subsequent cloning to be used in conjunction with the replication, transcription and translation of genes for production of DNA, RNA, ***and polypeptides***." (*Id.* at 1:41-46 (emphasis added)).

74. Contrary to Dr. Fiddes' and Dr. Gentz's opinions, it is my opinion that when Bujard is read in full, the nexus between the vectors in Bujard and recombinant antibody production are clear: the method described in Bujard is directed at the robust expression of polypeptides, not simply the narrow issue of stably cloning strong promoters into plasmids. (*See* Ex. 2019, Fiddes Decl. ¶ 157). In fact, the '415 patent confirms the relationship between promoters and recombinant DNA production, including the importance of stable promoters to constructing effective vectors. (*See* Ex. 1001, 9:3-15 (describing the "promoters most commonly used in recombinant DNA construction" and citing several publications that "enabl[ed] a skilled worker to ligate them functionally with plasmid vectors")).

75. It appears that, in this *inter partes* review, Dr. Fiddes takes a more narrow view of Bujard that he has in prior proceedings. For example, in his report in *Bristol-Myers Squibb Co. v. Genentech, Inc.*, No. 13-cv-05400 (C.D. Cal.), Dr. Fiddes stated that "Bujard *et al.*'s focus was on finding and using strong promoters to drive transcription of *DNA sequences encoding a protein of interest introduced into a host cell by recombinant DNA techniques* without interfering with expression of the marker used to select transformants." (Ex. 1144, Fiddes BMS Report ¶ 99 (emphasis added)). It is my opinion that the Board was correct in previously finding, and as Dr. Fiddes previously acknowledged, the "strategy described in Bujard 'provides a vehicle which can be used with one or more hosts for gene expression.'" (Ex. 2003, IPR2015-01624, Paper 15 at 11).

76. I also disagree with Patent Owners' suggestion that Bujard's subsequent history somehow impacts or limits the scope of Bujard's express teachings to a person of ordinary skill in April 1983. In particular, Patent Owners point to the fact that Stanford University allegedly "allowed" Bujard to expire in 1989. (Paper 31, Patent Owners' Response at 25). Even if true, I do not find Bujard's subsequent history to be relevant to Bujard's teachings or to have any bearing on the question of whether Bujard in combination of either Southern or Riggs & Itakura rendered the Challenged Claims obvious. It is also my opinion that a person of ordinary skill in the art would similarly find Bujard's subsequent history

irrelevant. Not only would it be speculative to assume the reason the patent expired, but any developments in 1989 are by definition beyond the knowledge of a person of ordinary skill in the art in 1983. The relevant question is what a person of ordinary skill in the art would understand Bujard to teach as of April 7, 1983, and the independent decisions by Bujard's assignee six years later do not impact that analysis.

B. Bujard Teaches the Use of the Co-Expression of Multiple, Distinct Eukaryotic Genes of Interest in a Single Host Cell

77. I disagree with Dr. Fiddes' and Dr. Gentz's opinions that Bujard does not teach or suggest the co-expression of multiple genes of interest in a single host cell. (*See, e.g.*, Paper 31, Patent Owners' Response at 24-25; Ex. 2019, Fiddes Decl. ¶¶ 170-189; Ex. 2021, Gentz Decl. ¶¶ 26, 30-32, 37). As I explain below, Bujard teaches the use of more than one eukaryotic genes of interest in a single host cell.

1. The Structure of the Bujard Vector Allows for the Co-Expression of Multiple Distinct Genes of Interest in a Single Host Cell

78. The vector as described in Bujard is generally comprised of four distinct sections: (1) a strong promoter, (2) a "DNA sequence of interest" encoding the protein(s) of interest, (3) a balanced terminator, and (4) a marker gene. (Ex. 1002, 2:3-20). The vector is then transformed into a host cell—either a microorganism or mammalian cell—with the goal of optimizing the production of recombinant proteins encoded by the DNA sequence of interest.

79. The DNA sequence of interest is inserted between the promoter and terminator to "provide for efficient transcription and/or expression of the sequence." (*Id.* at 2:33-38). Bujard uses several terms and/or phrases to describe the DNA sequence of interest, including the "gene of interest" (*id.* at Abstract), "a DNA sequence from a source other than the source of the promoter as a bridge between the strong regulatory signal sequences" (*id.* at 2:66-68), "the desired gene(s)" (*id.* at 8:6), and "a structural gene" (*id.* at 11:32). Nevertheless, Bujard explains that the "DNA sequence of interest" is usually comprised of "structural genes," which are genes that provide "RNA e.g., ribosomal or messenger, or [ ] a poly(amino acid)." (*Id.* at 2:33-38, 3:12-14).

80. Importantly, Bujard explains—more than once—that one or more genes of interest may be present in the "DNA sequence of interest" section of the vector. Specifically, Bujard states that "[t]he promoter and terminator may be separated by more than one gene, that is, a plurality of genes, including multimers and operons." (*Id.* at 3:46-48). Bujard also states that "one or more structural genes may be introduced between the promoter and terminator." (*Id.* at 7:61-63).

81. Dr. Fiddes and Dr. Gentz opine that the "one or more genes of interest" comprising the DNA sequence of interest are limited to multiple copies of the same gene. (*See, e.g.*, Paper 31, Patent Owners' Response at 31; Ex. 2019,

Fiddes Decl. ¶ 170). I disagree. In my opinion the Bujard clearly teaches the co-expression of multiple, distinct genes of interest.

2. Bujard's Reference to "Multimers" Does Not Limit Bujard to Multiple Copies of the Same Gene

82. To support his opinion that Bujard is limited to a single gene, Dr. Fiddes points to Bujard's reference to "multimers," which Dr. Fiddes concludes a person of ordinary skill in the art would have understood to mean "a construct having multiple copies of the same gene." (Ex. 2019, Fiddes Decl. ¶ 170). According to Dr. Fiddes, Bujard's reference to "'multimers' is clearly a reference to a type of DNA, not a type of protein." (*Id.* ¶ 174; *see also* Paper 31, Patent Owners' Response at 31). Again, I disagree.

83. Notably, Dr. Fiddes does not (and cannot) identify any express language in Bujard that justifies the limitation he seeks to read into the claims. In fact, Dr. Fiddes acknowledges that the ordinary meaning of the term "multimer" refers to a "multimeric protein," meaning a protein with more than one subunit. (Ex. 2019, Fiddes Decl. ¶ 174). However, Dr. Fiddes concludes that—in Bujard—"the only plausible interpretation of 'multimers' is multiple copies of the same gene." (*Id.*). Dr. Gentz similarly opines that "multimers" refers to "repeating units of the same gene." (Ex. 2021, Gentz Decl. ¶ 43).

84. In my view, Dr. Fiddes and Dr. Gentz seek to limit Bujard in a way that is not supported by the express language of Bujard, or by the state of the art in

April 1983. According to Dr. Fiddes, the *absence* of express language in Bujard specifying that the term "multimer" refers to different genes of a multimeric protein (*i.e.*, it's common usage) means that it is limited to multiple repeating units of the same gene or plasmid: "If the term were being used to describe the expression product of the DNA, and not the DNA itself, then Bujard would have said so using those express terms." (Ex. 2019, Fiddes Decl. ¶ 182). Similarly, Dr. Gentz states that "there is no suggestion … of inserting different eukaryotic genes and an additional promoter/terminator cassette into the plasmids." (Ex. 2021, Gentz Decl. ¶ 47).

85. In support of their proposed interpretation of Bujard's reference to "multimers," Dr. Fiddes and Dr. Gentz rely on publications other than Bujard. (Ex. 2019, Fiddes Decl. ¶¶ 175-78; Ex. 2021, Gentz Decl. ¶¶ 44-46). In my opinion, these publications undermine the express language of Bujard, which does not limit the term to multiple copies of the same gene. Nor do I believe that these references accurately reflect the state of the art in April 1983.

86. In fact, some of the proffered publications do not even use the word "multimer." For example, Dr. Gentz relies on a 1984 publication authored by Shi-Hsiang Shen, but that publication does not even include the word "multimer." (*See* Ex. 2021, Gentz Decl. ¶ 45; *see also* Ex. 2070 (Shen); Ex. 1114, Gentz Dep. at 136:9-137:4). Dr. Gentz also cites a 1986 publication by Brigitte von Wilcken-

Bergmann, but that publication also does not include the word "multimer." (*See* Ex. 2021, Gentz Decl. ¶ 45; *see also* Ex. 2071 (von Wilcken-Bergmann); Ex. 1114, Gentz Dep. at 140:6-13). Not only are these publications dated *after* the relevant time period (April 7, 1983), but they do not even include the very word that Dr. Gentz seeks to construe. As a result, I do not believe that these references undermine the express language of Bujard, which does not limit the term "multimer" as Dr. Fiddes and Dr. Gentz seek to do.

87. For substantially the same reasons, I do not find Dr. Gentz's or Dr. Fiddes' reliance on Hermann Bujard's European patent (Ex. 2005 (EP 1 532 260 B1)) to advance their strained definition of "multimer" in Bujard. (*See* Ex. 2021, Gentz Decl. ¶ 44; Ex. 2019, Fiddes Decl. ¶ 176). Specifically, Dr. Gentz and Dr. Fiddes point to the European patent's description of a "vector … wherein the transcription unit comprises a multimer of *tet*O sequences flanked on each site by a construction comprising an enhancerless promoter and a gene of interest." (Ex. 2005, claim 3). Dr. Gentz and Dr. Fiddes conclude that this language indicates that Bujard refers to a multiple copies of the same gene. (*See* Ex. 2021, Gentz Decl. ¶ 44; Ex. 2019, Fiddes Decl. ¶ 176). I disagree. Even setting aside that the European patent was filed approximately twenty years after the '415 patent, the language of the European patent does not advance Patent Owners' construction of "multimer" as it *does not refer to multiple copies of the same gene*.

88. Contrary to Dr. Fiddes and Dr. Gentz, it is my opinion that a person of ordinary skill would understand the use of the term "multimer" in Bujard to mean genes encoding multimeric proteins, including either multiple copies of the same gene *or* multiple distinct genes. My opinion is supported by the common use of the term, which Dr. Fiddes acknowledges (Ex. 2019, Fiddes Decl. ¶ 174)), as well as contemporaneous literature as of April 1983.

89. For example, in July 1982, Edward Baptist, Scott Hallquist, and Nicholas Kredich published an article in the Journal of Bacteriology describing the identification of a 34,500-Dalton polypeptide chain that was the product of the *cysB* gene, which "consists of a single cistron which codes for a protein that functions as an element of positive control." (Ex. 1100, Baptist, E. et al., *Identification of the Salmonella typhimurium cysB Gene Product by Two-Dimensional Protein Electrophoresis*, J. Bacter. 151:495-499 (July 1982)). After performing a chromatography experiment, the authors concluded that "the native *cysB* protein is a **multimer** of at least two and probably four or more subunits." (*Id.* at 495 (emphasis added)).

90. Similarly, in May 1982, Deane Mosher, Mary Jean Doyle, and Eric Jaffe published an article in the Journal of Cell Biology summarizing research into whether a particular glycoprotein secreted by human umbilical vein endothelial cells (GP-160) is the same as a specific glycoprotein (thrombospondin) that

"appears to play an important role in mediating platelet aggregation by binding to a specific receptor on other platelets" in response to thrombin. (Ex. 1101, Mosher, D. et al., *Synthesis and Secretion of Thrombospondin by Cultured Human Endothelial Cells*, J. Cell Biol. 93:343-348 (May 1982)). The authors describe thrombospondin as a protein "composed of three large disulfide-linked subunits," and GP-160 as "a disulfide-bonded **multimer** of 160-kdalton subunits," and ultimately conclude that "GP-160 is identical or nearly identical to thrombospondin." (*Id.* at 343 (emphasis added)).

91. Indeed, in my own work during the 1970s, I published multiple articles on the structure of chromatin, which is the protein and DNA material that forms the chromosomes of eukaryotic cells. These publications, which would also have formed part of the state of the art, describe the interaction between different types of histones (basic proteins) within chromatin. In particular, these publications describe the discovery that different types of histones associate into a tetramer composed of two subunits of different types of histones, (Ex. 1102, Kornberg, R., *Chromatin Structure: Oligomers of the Histones*, Science 184:865 (1974); Ex. 1103, Kornberg, R., *Chromatin Structure: A Repeating Unit of Histones and DNA*, Science 184:868 (1974)), as well as an octamer composed of eight subunits of four different types of histones (Ex. 1104, Thomas, O. &

Kornberg, R., *An octamer of histones in chromatin and free in solution*, Proc. Nat'l Acad. Sci. USA 72:2626 (1975)).

92. Additionally, dictionaries published both before and after April 1983 make clear that a "multimer" would include genes encoding multimeric proteins. For example, the Dictionary of Biochemistry—published in 1975—defines "multimer" as an "[o]ligomer," which in turn is defined as "[a] protein molecule that consists of two or more polypeptide chains, referred to as either monomers or protomers, linked together covalently or noncovalently." (Ex. 1071, Stenesh, J., Dictionary of Biochemistry at 205, 220 (1975)). Similarly, Henderson's Dictionary of Biological Terms—published in 1979—defines "multimer" as "a protein molecule made up of several polypeptide chains." (Ex. 1105, Holmes, S., Henderson's Dictionary of Biological Terms at 274 (9th ed. 1979)). Notably, the definition of "multimer" has not changed, and the term is still defined as:

- "[o]ligomer," *i.e.*, "[a] protein molecule that consists of two or more polypeptide chains, referred to as either monomers or protomers, linked together covalently or noncovalently" (Ex. 1106, Stenesh, J., Dictionary of Biochemistry and Molecular Biology at 312, 333 (2nd ed. 1989));
- "a protein molecule made up of more than one polypeptide chain" (Ex. 1107, Dorland's Illustrated Medical Dictionary at 1206 (31st ed. 1990));

- "a union of two or more organic macromolecules, like a union of several polypeptides forming a multimeric protein, or a protein complex composed of several protein units" (Ex. 1108, Tirri, R. et al., Elsevier's Dictionary of Biology at 443 (1st ed. 1998));
- "[a] supramolecular complex consisting of two or more identical or non-identical subunits (monomers). For example, a protein molecule, made up of two or more individual polypeptide chains," (Ex. 1109, Kahl, G., The Dictionary of Gene Technology Terms at 305 (2001)); and
- "a protein molecule made up of two or more polypeptide chains, each referred to as a monomer" (Ex. 1110, King, R. et al., Dictionary of Genetics at 288 (7th ed. 2006)).

93. This commonplace usage of the term multimer is particularly evident in light of the identification of antibodies as an exemplar protein that could be produced by the Bujard method since, by definition, antibodies would require the assembly of complete heavy and light chains. (*See* Ex. 1002, 4:14-16, 4:30-36, 5:11-27). And none of these definitions support the Dr. Fiddes' and Dr. Gentz's narrow reading of Bujard, *i.e.*, that the term "multimer" is limited to multiple copies of the same gene. In fact, Dr. Fiddes admits that he did not consult any biochemistry dictionaries whatsoever in rendering his opinion on the meaning of the word "multimer." (Ex. 1113, Fiddes Dep. Tr. at 218:5-9).

94. Accordingly, Dr. Fiddes' and Dr. Gentz's definition of "multimer" is inconsistent with how the term was used before (and after) April 1983.

95. In this regard, I agree with the Board, which in my opinion correctly found that Bujard "suggests the incorporation of a plurality of structural genes encoding for the subunits of a multimeric protein … within a vector that would be placed in a single host cell." (Ex. 2003, IPR2015-01624, Paper 15, at 18-19).

3. Bujard's Reference to "More Than One Gene" Does Not Limit Bujard to a Single Gene of Interest

96. In further support of their single gene limitation, Dr. Fiddes also disagrees with the Board's finding that Bujard's reference to "more than one gene" and/or "one or more structural genes" suggests the co-expression of the subunits of a multimeric protein. (Paper 31, Patent Owners' Response at 33; Ex. 2019, Fiddes Decl. ¶¶ 185-89). Dr. Fiddes does not identify any express language in Bujard that justifies the limiting Bujard's teachings to expression of a single gene. In my opinion, the Board's finding was correct.

97. Bujard explains that "the promoter and terminator may be separated by more than one gene, that is, a plurality of genes, including multimers and operons." (Ex. 1002, 3:46-48). Bujard later reiterates this point, stating that "one or more structural genes may be introduced between the promoter and terminator." (*Id.* 7:61-63). According to Dr. Fiddes, a person of ordinary skill in the art would understand the phrase "one or more structural genes" to mean "multiple copies of

the same gene or a bacterial operon," (Ex. 2019, Fiddes Decl. ¶ 186), or "a multimer, an operon, or at most, a single gene of interest and a selectable marker," (*id.* ¶ 170).

98. I disagree with Dr. Fiddes. In my opinion, Dr. Fiddes' interpretation is inconsistent with Bujard's express language, which contemplates the potential use of *other* genes of interest. Specifically, Bujard states that the promoter and terminator be separated by "more than one gene, that is, a plurality of genes, including multimers and operons." (Ex. 1002, 3:46-48). Dr. Fiddes also states that "[t]o the extent that the person of ordinary skill in the art considered any other 'genes' to have been contemplated, it would have only been a selectable marker in tandem with a single gene of interest." (Ex. 2019, Fiddes Decl. ¶ 186). Again, I disagree with Dr. Fiddes' opinion.

99. Dr. Fiddes' reading, which limits the phrase to multiple copies of the same gene *or* an operon, is premised on the incorrect assumption that "including" is not an open-ended term, *i.e.*, that the word "including" excludes the existence of genes of interest other than multimers and operons. In my opinion, a person of ordinary skill in the art would understand the word "including" to be open-ended. In the context of Bujard's statement that the promoter and terminator may be separated by a "plurality of genes, including multimers and operons," (Ex. 1002, 3:46-48), I understand Bujard to teach that multimers and operons are only two of

the "plurality of genes" that may be located on the vector between the promoter and terminator; in other words, there are other genes that may be placed in such a location. In any event, Dr. Fiddes admits that an "operon" is "a bacterial construct … that has a common promoter that direct transcription of … multiple genes into a single messenger RNA," and that "multiple genes" could be different genes. (Ex. 1113, Fiddes Dep. Tr. at 223:18-224:3).

100. Contrary to his opinion in this *inter partes* review, I understand that Dr. Fiddes has a similar interpretation of the word "including" when describing matters other than Bujard. Specifically, I understand that Dr. Fiddes changed the wording of his declaration in this *inter partes* review as a result of questioning he received in IPR2015-01624. In that proceeding, Dr. Fiddes' declaration stated that he has experience as an "independent consultant on biopharmaceutical matters for a variety of organizations, including the California Antiviral Foundation and the Institute for One World Health." (Ex. 1145, IPR2015-01624, Fiddes Decl. ¶ 12 (emphasis added)). At his deposition, Dr. Fiddes was questioned about whether his use of "including" indicated that he consulted for *more than* the two organizations listed. Subsequently, for this *inter partes* review, Dr. Fiddes changed the wording of his declaration to state that he has experience as an "independent consultant on biopharmaceutical matters for a variety of companies, and for two non-profit organizations, the California Antiviral Foundation and the Institute for One World

Health." (Ex. 2019, Fiddes Decl. ¶ 12 (emphasis added)). In my opinion, Dr. Fiddes' own actions with respect to his listed experience contradict his proffered opinion of the word "including." Specifically, if Dr. Fiddes' proffered interpretation of the word "including" was correct, there would have been no reason for him to change the way he listed his experience on his CV.

101. Dr. Fiddes also states that "one or more structural genes" "could also be interpreted to include a specific embodiment involving a single gene of interest and a selectable marker inserted between the promoter and terminator," given that during prosecution the Bujard inventors provided an example directed to only one gene of interest. (*Id.* ¶¶ 188-89). To the extent that Dr. Fiddes considers this a limitation on Bujard, I disagree. In my opinion, based on the structure of the Bujard vector, the marker is separate and distinct from the one or more structural genes. (*See, e.g.*, Ex. 1002, 2:13-16, 3:4-14, 7:57-63).

102. Dr. Fiddes' opinion is based on a selective reading of the Bujard prosecution history. In particular, Dr. Fiddes admits that he did not consider other parts of the Bujard prosecution history that contemplate the use of two structural genes, one prior to the terminator and one subsequent to the terminator in the direction of transcription. (Ex. 1113, Fiddes Dep. Tr. at 209:10-18).

103. Notably, Dr. Gentz agrees with me that a person of ordinary skill would have understood this language in Bujard to suggest the presence of multiple

genes downstream of the promoter. For example, Dr. Gentz explained that a person of skill in the art reading Bujard would understand that you could put multiple copies of the gene encoding for interferon, multiple Shine-Dalgarno sequences, and multiple stop codons downstream from the promoter and operator. (Ex. 1115, IPR2015-01624, Gentz Dep. Tr. at 148:24-152:13; Ex. 1141, IPR2015-01624, Gentz Dep. Ex. 5). Dr. Gentz also explained that a person of skill in the art reading Bujard would understand that you could put an operon between the promoter and the terminator, such as the lac operon—which itself consists of three structural genes (lacZ, lacY, and lacA), each of which is separated by a Shine-Dalgarno sequence and stop codon—with the operator between the promoter and the first gene (lacZ). (Ex. 1115, IPR2015-01624, Gentz Dep. Tr. at 153:3-157:20; Ex. 1142, IPR2015-01624, Gentz Dep. Ex. 6). Dr. Gentz further elaborated that a person of skill in the art reading Bujard would understand that you could put a marker gene, such as chloramphenicol acetyltransferase (CAT), and a gene of interest, such as a gene encoding for interferon, each separated by a Shine-Dalgarno sequence and stop codon, between the promoter and terminator. (Ex. 1115, IPR2015-01624, Gentz Dep. Tr. at 158:23-162:4; Ex. 1143, IPR2015-01624, Gentz Dep. Ex. 7).

4. Bujard's Reference to "Stop Codons" Does Not Limit Bujard to a Single Gene of Interest

104. Dr. Fiddes also point to Bujard's reference to "stop codons" to support a single gene limitation. I disagree with Dr. Fiddes, and it is my opinion that his opinion is premised on a misunderstanding of stop codons and the Bujard vector. Bujard teaches that the DNA sequence of interest may be followed by one or more stop codons: "Desirably, the gene is followed by one or a plurality of translational stop codons e.g. oop or nonsense codons, or preferably a plurality, usually up to about six, more usually from about two to five, where there is at least one stop codon in each reading frame." (Ex. 1002, 3:15-17). Bujard explains that the stop codons "aid in the efficiency of termination, both at the level of transcription and expression." (*Id.* at 3:19-21).

105. Dr. Fiddes claims that "the use of multiple stop codons does not imply multiple genes of interest." (Ex. 2019, Fiddes Decl. ¶¶ 192, 196; *see also* Paper 31, Patent Owners' Response at 36-37). Rather, according to Dr. Fiddes, the reference to stop codons "*could*" refer to "the use of a stop codon to separate multiple copies of a single eukaryotic protein of interest (as in the multimer example) or a eukaryotic protein of interest from a selectable marker." (Ex. 2019, Fiddes Decl. ¶ 195 (emphasis added)). I disagree with the underlying assumption that Dr. Fiddes' opinion relies, which is that the multiple stop codons concern a single reading frame. It is my opinion that a person of ordinary skill in the art would understand Bujard's

multiple stop codons to require multiple reading frames, translating different proteins. My opinion appears to be consistent with the Board's preliminary finding that a skilled artisan "would have found it obvious to insert the genes encoding for the heavy and light chains, separated by a stop codon, between the promoter and terminator sequences of the vector." (Ex. 2003, IPR2015-01624, Paper 15, at 19).

106. Dr. Gentz renders a similar opinion, stating that the reference to stop codons does not have "anything to do with the question of whether multiple different eukaryotic genes could be inserted in a plasmid" because the passage only "references a single gene." (Ex. 2021, Gentz Decl. ¶¶ 57-60). Again, Dr. Gentz appears to unduly limit the Bujard teaching and yet nowhere does Bujard state that the use of multiple stop codons must only refer to one gene. In fact, as cited above, he admitted otherwise on examination and himself depicted various scenarios in which multiple eukaryotic genes of interest could reside downstream from the promoter sequence in a Bujard plasmid, which scenarios could include multiple stop codons. *See supra*.

107. Patent Owners claim that the use of stop codons is similar to "pumping the brakes of a car when attempting to reduce speed going down a steep hill," but that is not how stop codons actually function. (Paper 31, Patent Owners' Response at 37). Rather, as the Board previously explained, stop codons act "[l]ike periods at the end of a sentence." (Ex. 2003, IPR2015-01624, Paper 15, at 19 n.7). In the

context of the Bujard vector, stop codons "signal the end of the polypeptide chain" such that "[w]hen a stop codon is reached [during translation], the polypeptide chain is complete and detaches from the ribosome." (*Id.*). The Board's explanation is correct, scientifically, and I agree with the Board's finding that the presence of multiple stop codons allows for "multiple structural genes to be translated into separate polypeptides." (*Id.* at 19).

C. Bujard Teaches a Method for Producing Antibodies

108. Dr. Fiddes opines that a person of ordinary skill would not have "singled out antibodies for production using Bujard's methods and materials." (Ex. 2019, Fiddes Decl. ¶ 207). Similarly, Dr. Gentz opines that "a scientist" would not have "concluded that the Bujard patent suggests coexpressing heavy and light chain genes as separate molecules in a single host cell, let alone that they could be assembled into a functional antibody." (Ex. 2021, Gentz Decl. ¶¶ 38-41).

109. I disagree with Dr. Fiddes and Dr. Gentz. To be clear, Bujard lists "a wide variety" of genes and "proteins of interest" that may be used with the vector, including "immunoglobulins e.g. IgA, IgD, IgE, IgG and IgM and fragments thereof." (Ex. 1002, 4:14-16, 4:30-36, 5:11-27). In other words—antibodies.

110. Neither Dr. Fiddes nor Dr. Gentz appear to debate the express reference to antibodies in the language of the patent. (Ex. 2019, Fiddes Decl. ¶ 202; Ex. 2021, Gentz Decl. ¶ 40). However, Dr. Fiddes opines that Bujard "does not 'specifically'

identify antibodies" because antibodies are "one of many proteins listed," and that there is "no reasonable basis to conclude that one of ordinary skill would have honed in on antibodies." (Ex. 2019, Fiddes Decl. ¶ 202). Dr. Gentz acknowledges that antibodies "theoretically could be considered for possible production," but opines that Bujard's express reference "is not a specific suggestion about antibodies or the ways in which they could be recombinantly produced." (Ex. 2021, Gentz Decl. ¶¶ 40-41).

111. Dr. Fiddes' and Dr. Gentz's opinions conflict with Bujard's clear language. Dr. Fiddes' position appears to be premised on the assumption that the Bujard inventors gave "little thought" to the list of proteins expressly identified in their patent. (Ex. 2019, Fiddes Decl. ¶ 218). In particular, Dr. Fiddes opines that the list of proteins in Bujard would be given less weight by a skilled artisan because the same list of proteins appears in other patents. (*Id.* ¶¶ 218-19). I disagree with Dr. Fiddes. In my opinion, a person of ordinary skill would not subscribe to such a view of express language in a patent.

112. Moreover, I disagree with Dr. Fiddes or Dr. Gentz to the extent they rely on the lack of successful attempts to make antibodies using recombinant methods, (*id.* ¶ 204; Ex. 2021, Gentz Decl. ¶¶ 40-41), or the "many serious problems to be solved before antibodies could be produced recombinantly" (Ex. 2019, Fiddes Decl. ¶¶ 205-07), in opining that Bujard did not suggest the production of antibodies.

As explained above, a person of ordinary skill would have been led by the prior art, common sense and a significant commercial motivation to make monoclonal antibodies.

113. The advent of the recombinant DNA technology, which took place well before April 1983, was a revolutionary development that allowed scientists to study molecular biology in ways that were not possible. By April 1983, a person of ordinary skill would have understood that recombinant DNA technology is generally applicable to proteins of all sizes and structures. Thus, the recombinant expression of an antibody does not require any specialized techniques compared to other types of proteins, *e.g.*, insulin.

114. Similarly, I disagree with Dr. Fiddes' opinion that Bujard's reference to "immunoglobulins" did not suggest the production of antibodies "given the size and complexity of antibodies, which the person of ordinary skill in the art would have understood to be among the most complex proteins on the Bujard list." (*Id.* ¶ 204). As explained above, in April 1983, it was widely assumed that virtually any protein, no matter how large or complex could be expressed using recombinant DNA technology. Thus, a person of ordinary skill would not have been deterred by the size and complexity of an immunoglobulin, and, in fact, would have had a reasonable expectation of successfully expressing the heavy and light chains in a single host

cell. Additionally, as I have discussed, contemporaneous evidence at the time confirms this conclusion.

115. Contrary to Dr. Fiddes' opinion, by April 1983, proteins even more complex than immunoglobulins had been produced using recombinant DNA techniques by co-expressing its constituent polypeptides as separate molecules in a single host cell. For example, in 1982 (before the filing of the '415 patent), scientists co-transformed two genes, *pyrB* and *pyrI*, in a single host cell using a single vector and demonstrated the resulting expression of a multimeric protein aspartate transcarbamylase, also known as ATCase. (*See, e.g.*, Ex. 1072, Pauza). As Dr. Fiddes admits, ATCase is an oligomer composed of six catalytic and six regulatory peptide genes, which is more subunits than found in an antibody. (Ex. 1113, Fiddes Dep. Tr. at 226:13-23, 228:4-14). ATCase has a molecular weight of 300,000 Daltons—nearly twice the size of a typical antibody. (Ex. 2019, Fiddes Decl. ¶ 43; Ex. 1113, Fiddes Dep. Tr. at 227:22-228:2). Dr. Fiddes, however, did not consider the 1982 Pauza article in rendering his opinions in this matter, despite admitting that ACTcase is "a multimeric protein consisting of different polypeptide chains that had been produced recombinantly … by expressing two different genes in a single host cell." (Ex. 1113, Fiddes Dep. Tr. at 229:10-16, 251:11-15).

D. Bujard Teaches the *In Vivo* Assembly of a Multimeric Protein Encoded by More Than One Gene in a Single Host Cell

116. Dr. Fiddes opines that Bujard does not suggest the *in vivo* assembly of a multimeric protein.

117. I disagree. Bujard is clear that there are at least two ways of obtaining the protein: (1) "as a single unit," or (2) "as individual subunits [ ] joined together in appropriate ways." (Ex. 1002, 4:19-21).

118. According to Dr. Fiddes, this statement simply "suggests [ ] that if expression of any proteins of interest were to be attempted, monomeric proteins could potentially be expressed as a single unit, whereas individual different subunits of a multimeric protein could potentially be expressed in separate host cells and joined *in vitro*." (Ex. 2019, Fiddes Decl. ¶ 227). Dr. Fiddes opines that "the only precedent for making multimeric eukaryotic proteins consisting of different polypeptide chains in a recombinant host cell at the time was insulin," and that, as a result, a person of ordinary skill in the art "would have tried the one-gene-per-host-cell approach that had been used successfully for insulin." (*Id.* ¶¶ 229-30).

119. In particular, Dr. Fiddes relies on the work of David Goeddel in the late 1970s in applying recombinant DNA technology to the production of insulin through a "one-polypeptide-per-host-cell approach." (*Id.* ¶¶ 83-87). Dr. Fiddes contends that Goeddel's work was followed by others, including Eli Lilly & Co., which "would have had a profound impact on the person of ordinary skill in the art." (*Id.*

¶¶ 88-90). Specifically, Dr. Fiddes cites a May 1983 publication by two Lilly scientists, B.H. Frank and R.E. Chance, that discusses two routes that Lilly "explored" for making insulin: (1) to "make the A and B chains in separate E. coli fermentations," and (2) to produce "proinsulin in a single E. coli fermentation and eventually to transform it to human insulin." (Ex. 2012, S15). Dr. Fiddes concludes that because the Lilly scientists "followed the first approach," so too would an ordinary person of skill in the art. (Ex. 2019, Fiddes Decl. ¶ 89).

120. I disagree with Dr. Fiddes, and in fact, in my opinion the reference that Dr. Fiddes cites contradicts his conclusion. First, as the publication makes clear, the two methods described—which Dr. Fiddes admits he did not review (Ex. 1113, Fiddes Dep. Tr. at 94:13-16)—were developed in ***1981***, not 1983. (Ex. 2012, S15, S20). Thus, the publication undermines Dr. Fiddes' assertion that the only method known as of April 7, 1983 was the "one-polypeptide-per-host-cell approach." In addition, the authors observed that "both methods," including the single cell method that Dr. Fiddes overlooks, "yield equivalent preparations of biosynthetic human insulin." (Ex. 2012, S15). Notably, Dr. Fiddes concedes (as he must) that the authors figured out how to process preproinsulin and separate it into the A and B chains to make functional insulin. (Ex. 1113, Fiddes Dep. Tr. at 93:13-94:1). The authors also developed methods for recovering the insulin produced by the one-cell method. As the publication explains: "The proinsulin is subsequently converted to

its S-sulfonate derivative by oxidative sulfitolysis and then isolated. Then the proinsulin-S-sulfonate is treated with a thiol reagent, beta-mercaptoethanol, which allows the proinsulin molecule to fold and form the proper disulfide bonds. Bonds as high as 70 percent are achieved in this process, which was also developed in The Lilly Research Laboratories." (Ex. 2012, S16).

121. It is my opinion that Dr. Fiddes' attempt to read into Bujard a limitation that only monomeric proteins be expressed as a single unit is contrary to the plain language of Bujard, but also contrary to what a person of ordinary skill would have understood Bujard to teach in April 1983. In my opinion, Bujard does not limit the term "single unit" to monomeric proteins, but rather states unequivocally that "[a] wide variety of structural genes are of interest for production of proteins" and that "[t]he proteins may be prepared as a single unit or as individual subunits and then joined together in appropriate ways." (Ex. 1002, 4:14-21). In my opinion, a person of ordinary skill would understand Bujard's reference to "single unit" to include the *in vivo* assembly of a multimeric protein (such as an antibody), and, where the proteins did not assemble into an antibody inside of the host cell, the "individual subunits" (*i.e.*, the heavy and light chains) would be "joined together" through *in vitro* assembly.

122. My opinion is consistent with the Board's finding that Bujard "suggests that the skilled artisan's mindset would include making multimeric proteins within a single host cell." (Ex. 2003, IPR2015-01624, Paper 15, at 20).

X. THE PATENT OWNERS' CHALLENGES TO THE BOARD'S PRELIMINARY FINDING THAT IT WOULD HAVE BEEN OBVIOUS TO COMBINE BUJARD WITH RIGGS & ITAKURA ARE WRONG

123. Patent Owners and Dr. Fiddes dispute the Board's preliminary finding that there is a reasonable likelihood that a skilled artisan would have found it obvious to combine Bujard's teachings "with the *in vitro* assembly technique taught by Riggs & Itakura … to produce an immunoglobulin molecule." (*Id.* at 18; *see also* Paper 31, Patent Owners' Response at 45-49; Ex. 2019, Fiddes Decl. ¶ 274). It is my opinion that a skilled artisan would have found it obvious to combine Bujard's teachings with Riggs & Itakura.

A. Riggs & Itakura Suggests the *In Vitro* Assembly of Heavy and Light Chains

124. According to Dr. Fiddes, Riggs & Itakura is simply a "review article summarizing a process for making insulin," and does not address the *in vitro* assembly of antibody chains. (Ex. 2019, Fiddes Decl. ¶¶ 243-44).

125. I disagree. Riggs & Itakura discusses the production of insulin from bacterial cells. Riggs & Itakura states that it is more than just "a review article that describes the Genentech/City of Hope approach to making insulin." (*Id.* ¶ 239). In

fact, the first sentence makes clear that Riggs & Itakura touches on recombinant DNA technology more generally: "Synthetic DNA chemistry is no longer an esoteric discipline without obvious practical applications. On the contrary, the combination of synthetic DNA chemistry, recombinant DNA techniques, and molecular cloning already has resulted in useful products—somatostatin and insulin—and promises much more." (Ex. 1003, at 531). Riggs & Itakura discusses synthetic DNA chemistry techniques and even suggests that such techniques could be used to express any polypeptide chain: "The techniques we used are quite general; thus we are confident that bacteria can be engineered to produce any peptide hormone that does not contain methionine. By using other cleavage tricks, or accepting lower yields, even peptides that contain methionine can probably be made." (*Id.* at 531-32).

126. The alternative "cleavage tricks" discussed in Riggs & Itakura were well known by April 1983, for example, known proteases that display highly restricted specificities, which decreases the likelihood that unwanted secondary cuts will occur. Certain proteases cut at very specific amino acid sequences that are not found in the amino acid sequences of the heavy or light chain, and those sequences can be engineered into the expression vector to allow cleavage at the appropriate location on the expressed precursor polypeptide.

127. Riggs & Itakura is an important publication that adds two important teachings to Bujard. First, Riggs & Itakura teaches hybridomas as a source of antibody genes. (*Id.* at 537-38). Riggs & Itakura describes a process in which two genes were inserted into separate host cells and expressed, with the resulting joined together *in vitro*. Second, Riggs & Itakura teaches the *in vitro* assembly of heavy and light chains. Riggs & Itakura explains that one of the potential applications of its recombinant DNA techniques is the production of antibodies, stating that "[h]ybridomas will provide a source of mRNA for specific antibodies. Bacteria may then be used for the production of the antibody peptide chains, which could be assembled in vitro and used for passive immunization." (*Id.*).

128. Dr. Fiddes dismisses the reference to "antibody example" as "speculation," (Ex. 2019, Fiddes Decl. ¶ 270), apparently requiring Riggs & Itakura to teach how to recombinantly produce antibodies. However, it is my understanding that that is not required. Rather, Riggs & Itakura, in combination with Bujard, must render obvious certain claims of the '415 patent. In this regard, my opinion is that a person of ordinary skill in the art would understand Riggs & Itakura to suggest the *in vitro* assembly of heavy and light chains, given the context of its teachings, its reference to hybridomas as a source of antibody genes, and its description of *in vitro* assembly. (*See* Ex. 1003, at 532, 537-38).

B. A Person of Skill in the Art Would Have Been Motivated to Combine Bujard with Riggs & Itakura

129. Dr. Fiddes opines that Riggs & Itakura and Bujard "address different things" and, therefore, a person of ordinary skill in the art would not have "combined Bujard with Riggs & Itakura for the specific purpose[ ] of making an antibody using recombinant methods." (Ex. 2019, Fiddes Decl. ¶¶ 245-46).

130. I disagree. Dr. Fiddes' opinion is based on a narrow view of both Riggs & Itakura and Bujard: "One, Riggs & Itakura, describes a process for making insulin that is deemed fit for scale up and commercialization. The other, Bujard, provides a research tool that can be used to clone strong promoters into plasmids." (*Id.* ¶ 245).

131. It is my opinion that a person of ordinary skill in the art would understand the scope and context of Riggs & Itakura to concern production of proteins in host cells. Riggs & Itakura makes clear that "the use of synthetic DNA provides the most specific and general approach to making directed changes in DNA." (Ex. 1003, at 533). Riggs & Itakura goes on to state that it "should be possible to repair or create mutations, convert a gene of one species to the same gene of another species, make genes for peptide analogues, create restriction sites, etc. Although practical applications have not yet been made, the feasibility of the approach has been demonstrated." (*Id.* at 533-35).

132. I disagree with Dr. Fiddes' opinion that a person of ordinary skill would not have been motivated to combine Riggs & Itakura and Bujard. As an initial matter, both Riggs & Itakura and Bujard are directed to the production of eukaryotic proteins in host cells. Indeed, Riggs & Itakura explicitly states that one of the "potential practical applications" of the method includes "Antibodies," explaining that "[h]ybridomas will provide a source of mRNA for specific antibodies. Bacteria may then be used for the production of the antibody peptide chains, which could be assembled in vitro and used for passive immunization." (*Id.* at 537-38). Moreover, building on Bujard's teaching that "individual subunits" of the desired protein product may be "joined together in appropriate ways," (Ex. 1002, 4:20-21), Riggs & Itakura discloses that the *in vitro* assembly technique is well-suited for the assembly of multiple subunit proteins, such as antibodies. As a result, a person of ordinary skill in the art would have understood that the heavy and light chains (*i.e.*, the "individual subunits" of an antibody) could be produced recombinantly pursuant to the Bujard method and assembled *in vitro* according to Riggs & Itakura.

133. Dr. Fiddes opines that Riggs & Itakura "teaches an approach to protein production that is the opposite of co-expressing multiple different chains of a multimeric protein in a single host cell." (Ex. 2019, Fiddes Decl. ¶ 250). Patent Owners and Dr. Fiddes conclude that combining Bujard with Riggs & Itakura

would "have led to a two host cell approach, not the single host cell invention of the challenged claims." (Paper 31, Patent Owners' Response at 44; *see also* Ex. 2019, Fiddes Decl. ¶ 250). I understand that Patent Owners advanced this same argument in IPR2015-01624, and I do not find any merit to their contention. Simply put, as the Board recognized, "[t]here is no support … for Patent Owners' contention that the *in vitro* assembly technique disclosed [in Riggs & Itakura] is only applicable when the polypeptide chains are produced in separate host cells." (Ex. 2003, IPR2015-01624, Paper 15 at 19-20).

134. Dr. Fiddes' opinion is based on the fact that "making an antibody using recombinant methods had never been done, and the reports in the literature showed tremendous variability and unpredictability in expressing even a single antibody chain." (Ex. 2019, Fiddes Decl. ¶¶ 248, 274-76; *see also* Paper 31, Patent Owners' Response at 49-52). Emphasizing the differences between insulin and antibodies, Dr. Fiddes opines that "[t]he larger size and complexity of an antibody as compared to insulin means the proper folding for an antibody presents a far more challenging task than insulin." (Ex. 2019, Fiddes Decl. ¶ 276).

135. I disagree with Dr. Fiddes' position. As I explained above, differences in the sheer size or complexity of antibodies and other proteins does not mean that a person of ordinary skill would not have had a reasonable expectation of successfully expressing the heavy and light chains in a single host

cell. The difficulty in expressing a recombinant protein is not correlated with the structure or size of the target protein. In fact, proteins larger than immunoglobulins had already been successfully expressed using recombinant DNA techniques. Thus, it is my opinion that a person of ordinary skill in the art would not have been deterred by the size and complexity of an antibody as compared to insulin, for example. Such a person would have been motivated to apply the known art to target antibodies for recombinant production.

C. A Person of Skill in the Art Would Have Had a Reasonable Expectation of Success in Combining Bujard with Riggs & Itakura

136. In my opinion, person of skill in the art would have had a reasonable expectation of success in combining Bujard with Riggs & Itakura. First, *in vitro* antibody assembly techniques were well known in the art. Indeed, the '415 patent uses prior art assembly techniques. (Ex. 1001 at 12:58-13:52). Second, prior to April 1983, it was well known that a host cell could assemble and produce functional antibodies, *in vivo*. Indeed, that work was published by Ochi et al. (Ex. 1021).

137. Third, Riggs & Itakura demonstrated that the separate chains of insulin could be joined *in vitro*, and they were of the opinion that the same or similar techniques could be used successfully for immunoglobulin chains made by recombinant DNA means in microorganism host cells. (Ex. 1003, at 531-32, 537-

38). There would have been no reason for a person of ordinary skill in the art to believe that the *in vitro* assembly methods in Riggs & Itakura could not also be successfully used to assemble the co-expressed heavy and light chains produced by Bujard's similar recombinant DNA methodologies. A person of ordinary skill in the art would therefore have had a reasonable expectation of success in combining Bujard with Riggs & Itakura to result in the subject matter of the Challenged Claims.

138. Finally, the "complication of 'inclusion bodies'" does not change my opinion that a person of ordinary skill would have had a reasonable expectation of success. (Paper 31, Patent Owners' Response at 51-52). Standard chemical means to isolate proteins from inclusion bodies were well known in April 1983. During this time, it was well-understood that when foreign or exogenous proteins were expressed in bacteria or other host cells using recombinant DNA techniques, the proteins often appeared as insoluble protein aggregates known as inclusion bodies. The host cell or cells must be lysed, or ruptured, to recover the inclusion bodies. Thereafter, these insoluble protein aggregates needed to be denatured and then renatured to permit the proper folding and reconstitution of the respective protein. Standard chemical means well-known in the art were employed for these denaturing and renaturing processes.

139. Denaturation refers to the disruption of protein aggregates, such as inclusion bodies, and the unfolding of the protein chains. The denaturation process has been accomplished since the 1970s by the addition of a chemical, such as guanidine hydrochloride. This process is still used today. Renaturation refers to refolding of protein chains and their recombination into multimers. The renaturation process is routinely accomplished by the gradual removal of the denaturing chemical agent. In proteins such as antibodies that contain disulfide bonds, the formation of these bonds will occur spontaneously upon refolding.

140. The '415 patent explains that after the anti-CEA heavy and light chains were co-expressed as insoluble inclusion, or "refractile," bodies, the *E. coli* host cell was ruptured, and the heavy and light chains were denatured under harsh reducing conditions. (Ex. 1001, columns 13, 25). These processes enabled the solubilization of the protein aggregates and the separate recovery of each protein chain. Thereafter, the chains were renatured in an oxidative environment which promoted the refolding and reconstitution of the chains into their assembled, tetrameric form. (*Id.*). This example in the '415 patent describes the exact processes that persons skilled in the art had been using for many years to reconstitute recombinant proteins.

141. In my opinion, the combination of Riggs & Itakura and Bujard renders the Challenged Claims of the '415 patent obvious.

XI. IT WOULD HAVE BEEN OBVIOUS TO COMBINE THE TEACHINGS OF SOUTHERN AND BUJARD

142. Patent Owners and Dr. Fiddes disagree with the Board's finding that Southern teaches "the general applicability of its disclosed co-transformation technique by 'inserting *genes of interest* into vector DNAs designed to express neo or gpt,'" and that there is a "reasonable likelihood that the skilled artisan would have found it obvious to use Southern's two-vector technique to express both the heavy and light immunoglobulin chains in a single host cell." (Ex. 2003, IPR2015-01624, Paper 15 at 22; *see also* Paper 31, Patent Owners' Response at 57-60; Ex. 2019, Fiddes Decl. ¶¶ 292-95). Based on Dr. Fiddes' opinions, Patent Owners assert that "Bujard and Southern address fundamentally different issues, and there would have been no reason in April 1983 for a skilled artisan to even consider their teachings together." (Paper 31, Patent Owners' Response at 55).

143. I disagree. In my view, Dr. Fiddes' position is based on an unreasonably narrow view of Southern and the state of the art in 1983. It is my opinion that the Board's preliminary findings regarding the Southern and its combination with Bujard are correct and that it would have been obvious to combine the teachings of Bujard and Southern.

A. Southern Discloses a Two-Vector Approach For Expressing More Than One Protein of Interest in a Single Host Cell

144. Patent Owners contend that "Southern does not disclose or suggest the 'single host cell' or the two vector limitations absent from Bujard." (Paper 31, Patent Owners' Response at 53). Dr. Fiddes similarly states that Southern "does nothing more than provide a new vector for use in mammalian host cells," and "does not provide additional inferences that would have suggested the use of multiple vectors to express distinct genes in a single host cell." (Ex. 2019, Fiddes Decl. ¶¶ 291, 293).

145. I disagree with Patent Owners and Dr. Fiddes. As an initial matter, Dr. Fiddes is incorrect that Southern "provide[s] a new vector." (*Id.* ¶ 291). The vector described in Southern—Prof. Berg's pSV2 vector—was described in several prior publications co-authored by Prof. Berg, including Prof. Berg's Nobel Lecture. (*See* Ex. 1069, Berg; Ex. 1120, Mulligan & Berg). Southern is the culmination of Prof. Berg's work developing the pSV2 vector; in Southern, the marker genes *neo* and *gpt* were inserted into the pSV2 vector, demonstrating the double transfection of the pSV2-gpt and pSV2-neo vectors. To the extent Dr. Fiddes and Patent Owners attempt to treat Southern in isolation from Prof. Berg's earlier work, I disagree because a person of ordinary skill would have aware of Prof. Berg's earlier work describing the development of the pSV2 vector. Indeed, that work is explicitly referenced in Southern. (*See, e.g.*, Ex. 1004, at 328, 331,

340). And, in the words of Dr. Fiddes, "when you read any patent or research paper, to understand it fully you need to understand the focus and what [it's] about. It's just part of understanding the document." (Ex. 1116, IPR2015-01624, Fiddes Dep. Tr. at 70:10-13). Because Dr. Fiddes and Patent Owners do not consider Prof. Berg's earlier work describing the development of the pSV2 vector, they distort the teachings of Southern.

146. Prof. Berg designed the pSV2 vector to "introduce and maintain new genetic information in a variety of mammalian cells." (Ex. 1069, at 300). To do so, Prof. Berg designed the pSV2 vector such that it contained a selectable marker and multiple restriction sites that could accommodate one or more genes of interest. (*Id.*). These basic design features are reflected in Fig. 2 of Southern. (Ex. 1004, at 332). Initially, Prof. Berg used the bacterial gene *gpt* as his selectable marker. (*Id.* at 328). As explained in Southern, the Berg lab used a pSV2 vector containing a *gpt* selectable marker (designated pSV2-gpt) to show that a variety of eukaryotic genes of interest could be expressed in mammalian cells. (*Id.*). The purpose of the work in Southern was to first demonstrate the viability a new selectable marker, the *neo* gene, and second to show that vectors containing the *gpt* and *neo* selectable could be co-transformed into a single host cell. By the time the Southern paper was published, the ability of the pSV2 vector to express genes of interest had already been well established. Thus, Patent Owners' argument that

"Southern does not disclose any experiment involving even a single protein of interest" (Paper 31, Patent Owners' Response at 53) does not impact the obviousness analysis. Based on Southern's description of Prof. Berg's prior work on the pSV2 vector and the references cited by Southern, a person of ordinary skill would have readily understood that the pSV2-gpt and pSV2-neo vectors described in Southern could each be used to express genes of interest. Indeed by April 1983, both a pSV2-gpt and pSV2-neo vector had been used to express an antibody light chain in a eukaryotic host cell.

147. Given this background, I disagree with Dr. Fiddes' opinion that "Southern does not provide additional inferences that would have suggested the use of multiple vectors to express distinct genes in a single host cell." (Ex. 2019, Fiddes Decl. ¶ 293). As Southern explains, the ability to co-transform a single host cell with a pSV2-gpt vector and pSV2-neo vector allows for "double and dominant" selection. (Ex. 1004, at 339). A person of ordinary skill would have readily recognized that "double and dominant selection" permits the ability to two introduce two different genes, one on each vector, into a single host cell. Indeed, the whole purpose of having different selectable markers is to provide the ability to select for double transformants and in turn the purpose of employing a double transformant is to introduce two different genes of interest. Consistent with this understanding, I note that a group led by Sherie Morrison used the exact double

transformation technique described in Southern to express an antibody heavy and light chain in a single cell by not later than October 1983. (*See* Ex. 1111; Ex. 1112; Ex. 1147; Ex. 1150).

148. For similar reasons, I disagree with Patent Owners and Dr. Fiddes assertion that Southern's discussion of co-transformation of "genes of interest" "merely refers to the vector's ability to express various types of genes, depending upon which particular gene is desired—not multiple different genes at the same time." (Paper 31, Patent Owners' Response at 54; Ex. 2019, Fiddes Decl. at ¶¶ 302-304). This argument once again ignores the purpose behind using the double transformation technique disclosed by Southern. If a person of ordinary skill wanted to express only a single gene of interest, there would be no reason to employ Southern's co-transformation technique.

149. Finally, I disagree with Patent Owners' argument that "Southern described the need for future experimentation regarding some undisclosed use for the two-vector approach." (Paper 31, Patent Owners' Response at 59). Again, this argument ignores the fact that the ability of the pSV2 vector to express genes of interest had already been established. The data in Southern showing that co-transformation of the pSV2-neo and pSV2-gpt in a single host cell is possible is the experimentation that is necessary to use the two-vector approach. I also disagree with Patent Owners' arguments that the ten-fold reduction in the number of stable

transformants reported by Southern for the co-transformation technique would have made the two-vector approach non-obvious. (*Id.* at 57). As Southern explains, the reduction in stable transformants was likely caused by the stress of both selectable markers acting at once. (Ex. 1004, at 337). A person of ordinary skill would understand that seeing ***any*** significant number of stable transformants, which Southern clearly shows, indicates that the experiment was a success and the reduction in the number of transformants simply means that the host cell culture would need to be grown for a longer period of time before the proteins encoded by the genes of interest could be recovered.

B. A Person of Ordinary Skill in the Art Would Have Had Good Reason to Combine Bujard With Southern

150. Dr. Fiddes opines that "the person of ordinary skill in the art would not have been motivated from the combination of Southern and Bujard to co-express antibody heavy and light chains in a single host cell using separate plasmids." (Ex. 2019, Fiddes Decl. ¶ 306).

151. I disagree. In my opinion, there are several reasons why a person of ordinary skill would have been motivated to combine the teachings of Southern and Bujard. Southern and Bujard are both directed to a general method of recombinantly expressing proteins in a eukaryotic host cell. Southern discloses a two-vector approach that is optimally suited for expressing more than one protein of interest in a single host cell. It teaches a direct and efficient way to

independently express both the heavy and light chains in a single host cell because cells containing both vectors can be readily identified via different selectable markers and the genes encoding proteins of interest are under the control of separate promotors. A person of ordinary skill would have readily recognized that Southern's dual vector system would be the ideal platform for recombinantly expressing "antibodies," (*i.e.*, more than one protein of interest) as taught by Bujard. A skilled artisan would have readily been able to use the expression systems developed by Southern with Bujard's teaching to produce a functional antibody in a single host cell by co-expressing the heavy and light chains as separate molecules.

152. I also understand that Patent Owners have suggested that the "uncertainties … surrounding recombinant DNA techniques—and the production of antibodies in particular—forecloses any argument that a skilled artisan would have reasonably expected success" in producing functional antibodies using two of Southern's vectors in a single host cell. (Paper 31, Patent Owners' Response at 61). Dr. Fiddes similarly opines that neither Bujard nor Southern "attempts to provide any information regarding how an antibody should be made using recombinant means and neither attempts to answer the many questions that remained unanswered at the time regarding antibody gene regulation and control, and the uncertainty and unpredictability seen even with attempts to produce single

antibody chains." (Ex. 2019, Fiddes Decl. ¶ 316). Patent Owners appear to conclude that because Southern does not demonstrate the expression of any proteins of interest, it is of limited value. (Paper 31, Patent Owners' Response at 56-57).

153. I disagree with this conclusion. Southern, in combination with Bujard, suggests the use of a two-vector technique to express both the heavy and light immunoglobulin chains in a single host cell. In my opinion, a person of ordinary skill would have had a reasonable expectation of success in using two-vectors to express the heavy and light chains in a single host cell. By April 1983, both the pSV2-neo and pSV2-gpt vectors described by Southern had been used to express eukaryotic proteins in a eukaryotic host cell. Indeed, Southern itself demonstrates that these two vectors can be used to express multiple proteins in a single host cell. These past successes would have led a person of ordinary skill to believe that the heavy and light chains could likewise be expressed via Southern's two-vector system, and there is nothing about the heavy and/or light chains that would have caused a person of ordinary skill to think any differently.

154. Dr. Fiddes opines that a person of ordinary skill would not have "looked at Bujard and Southern together to arrive at any solutions regarding the recombinant production of proteins as they disclose expression constructs that would not be compatible in the host expression systems which are the focus of the

other reference." (Ex. 2019, Fiddes Decl. ¶ 286). Specifically, Dr. Fiddes states that "Bujard focuses on bacterial expression systems," whereas Southern focuses on "a mammalian expression system," and thus "the pSV2 system described in Southern would not be expected to express eukaryotic genes of interest in a bacterial host cell." (*Id.* ¶¶ 287-88). I disagree.

155. Bujard provides express motivation to apply its teachings to mammalian cells: "Higher cells, e.g., mammalian, may also be employed as hosts, where viral, e.g., *bovine papilloma virus* or other DNA sequence is available which-has plasmid-like activity." (Ex. 1002, at 6:34-37 (emphasis added)). Southern teaches expression vectors using a viral promoter, SV40, to express the multiple genes of interest and the vectors described in Southern have "plasmid-like activity." (Ex. 1004, at 327). Thus, the fact that Bujard and Southern focus on bacterial expression systems and mammalian expression systems, respectively, would not have discouraged a person of skill in the art from combining Bujard and Southern. Bujard teaches it explicitly and a person of ordinary skill would certainly understand this teaching in the context of recombinant DNA techniques known at the time.

156. Dr. Fiddes also opines that a person of skill in the art would not have been motivated to apply the teachings of Bujard to the Southern to express the

heavy and light chain in a single cell. (Ex. 2019, Fiddes Decl. ¶¶ 292-314). For reasons explained above, I disagree.

157. Southern teaches the use of a two vector system—the pSV2-gpt vector and the pSV2-neo vector—in a single host. A person of ordinary skill would have recognized that this two-vector approach was specifically designed to express different proteins of interest in a single host cell. Indeed, expressing two different proteins of interest is one of the primary reasons why a researcher would want to insert two different vectors, with separate selectable markers, into a single a host cell. Moreover, using two vectors allows the independent expression of more than one protein of interest in a single host cell. This is because the genes coding for the multiple proteins of interest are under the control of separate promoters. Thus, a person of ordinary skill would have also been motivated to combine Southern and Bujard because they both describe techniques for expressing eukaryotic proteins in a eukaryotic host cell and their techniques are compatible with one another.

C. A Person of Ordinary Skill in the Art Would Have Had A Reasonable Expectation of Success in Combining Bujard With Southern

158. I understand that Patent Owners have argued that "[a] person of ordinary skill would not have had a reasonable expectation that functional antibodies could be produced using two of Southern's vectors in a single host cell"

based on Dr. Fiddes opinions that purported uncertainties in April 1983 about "how the expression of immunoglobulin genes was regulated and whether such expression would occur." (Paper 31, Patent Owners' Response at 61; Ex. 2019, Fiddes Decl. ¶¶ 307-17).

159. I disagree. Prior to April 1983, Ochi I showed successful recombinant expression of the light chain, using the pSV2-neo vector in cell lines expressing only the native heavy chain. (Ex. 1021, at 596). The cells expressing the recombinant light chain produced functional antibodies. Based on this work alone, a person of ordinary skill in the art would have had a reasonable expectation of success expressing both the heavy and light chain in a single cell. In addition to Ochi I (Ex. 1021), the Oi (Ex. 1031) and Rice & Baltimore (Ex. 1020) publications, both expressing light chain in a myeloid cell line, would have further provided a person of ordinary skill in the art with a reasonable expectation of success.

160. Further, Southern itself provides a reasonable expectation of success. Southern validates the ability to use two vectors, each having a different selectable marker, and explains that the two-vector system could be used to express two proteins of interest in a single host cell: "[c]otransformation with nonselectable genes can be accomplished by inserting genes of interest into vector DNAs designed to express *neo* or *gpt*." (Ex. 1004, at 339).

161. I understand that there is no requirement for absolute predictability of success—all that is required is a reasonable expectation of success. However, it is my opinion that the state of the art at the time, as evidenced by Ochi I (Ex. 1021), Oi (Ex. 1031), Rice & Baltimore (Ex. 1020), and Southern itself, provided near certainty that expressing both the heavy and light chain would result in successful production of functional antibodies.

162. Thus, it is my opinion that a person of ordinary skill in the art would have had a reasonable expectation of success in combining Bujard with Southern.

D. Patent Owners' Arguments That Southern Cannot Invalidate Claims 1, 2, and 33 Are Wrong

163. I understand that Patent Owners have argued that the combination of Bujard and Southern would not have rendered claims 1, 2, and 33 obvious, because those claims require producing an assembled antibody, and neither Bujard nor Southern allegedly teach antibody assembly. I disagree. First, Bujard explicitly teaches that "immunoglobulins" can be made using the recombinant techniques disclosed in Bujard. An "immunoglobulin" is an assembled antibody, not simply recombinantly-expressed heavy and light chains. A person of ordinary skill in the art would have known how to assemble a heavy and light chain into a functional antibody using well-known *in vitro* assembly techniques. Indeed, the '415 patent references these prior art assembly techniques. (Ex. 1001, 12:58-13:52). Second, the work of both Ochi et al. and Oi et al. demonstrated the ability to transform

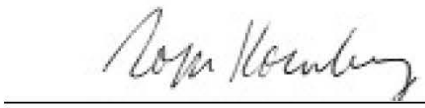
Prof. Berg's pSV2 vectors into lymphoid cells. (Ex. 1021; Ex. 1031; Ex. 1040). Lymphoid cells naturally assembly heavy and light chains into functional antibodies. A person of ordinary skill would have understood that using a lymphoid cell as the host cell would result in *in vivo* assembly of the heavy and light chains.

164. Accordingly, in my opinion, the combination of Southern and Bujard renders the Challenged Claims of the '415 patent obvious.

XII. CONCLUSION

165. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made 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.

Executed this 7th day of April 2017. I declare under penalty of perjury that the foregoing is true and correct.



Roger D. Kornberg

Exhibit A

Curriculum Vitae

ROGER D. KORNBERG
Winzer Professor in Medicine
Department of Structural Biology
Stanford School of Medicine
Stanford, CA 94305

BORN:	April 24, 1947 - St. Louis, Missouri
FAMILY:	Married to Prof. Yahli Lorch; children Guy, Maya, Gil

EDUCATION:

1967	B.S. Harvard University, Chemistry
1972	Ph.D. Stanford University, Chemistry

PROFESSIONAL EXPERIENCE:

1972-1973	Postdoctoral Fellow, MRC Laboratory Cambridge, England
1973-1974	Junior Fellow, Society of Fellows of Harvard University MRC Laboratory of Molecular Biology, Cambridge, England
1974-1975	Member of Scientific Staff, Division of Cell Biology MRC Laboratory of Molecular Biology, Cambridge, England
1976-1977	Assistant Professor of Biological Chemistry Department of Biological Chemistry Harvard Medical School
1978-present	Professor of Structural Biology Department of Structural Biology Stanford University, School of Medicine
1984-1992	Chairman and Professor of Structural Biology Department of Structural Biology Stanford University, School of Medicine

HONORS:

1981	Eli Lilly Award
1982	Passano Award
1990	Ciba-Drew Award
1997	Harvey Prize, The Technion, Israel
2000	Gairdner International Award, Gairdner Foundation, Canada (shared with R. Roeder)
2001	Hoppe-Seyler Award, Society for Biochemistry and Molecular Biology, Germany
2001	Honorary degree, Hebrew University of Jerusalem, Israel
2001	Welch Award in Chemistry, Welch Foundation

2002	Merck Award, American Society for Biochemistry and Molecular Biology (shared with R. Roeder)
2002	Le Grand Prix Charles-Leopold Mayer, Academie des Sciences, France
2003	Pasarow Award in Cancer Research
2003	Honorary degree, University of Umea, Sweden
2003	Massry Prize (shared with M. Grunstein and D. Allis)
2005	General Motors Cancer Research Award (Sloan Prize)
2006	Dickson Prize, University of Pittsburgh
2006	Louisa Gross Horwitz Prize, Columbia University
2006	Nobel Prize in Chemistry
2008	Aharon Katzir-Katchalsky Award of the IUPAB
2008	Ahmed Zewail Prize, Wayne State University
2008	Honorary Professor, Peking University
2008	Honorary degree, University of Regensburg, Germany
2009	Honorary degree, Bar-Ilan University, Israel
2010	Pauling Legacy Award
2010	Santiago Grisolia Prize, Valencia, Spain
2011	Frank Westheimer Prize, Harvard University
2012	Honorary degree, St. Petersburg Academic University
2013	FEBS medal

MEMBERSHIPS:

1993	National Academy of Sciences
1995	Japanese Biochemical Society (hon.)
1998	American Academy of Arts and Sciences
2003	Foreign Associate, European Molecular Biology Organization
2007	Royal Society of Chemistry (hon.)
2008	American Philosophical Society
2009	Foreign Member, the Royal Society
2012	Foreign Member, Korean Academy of Science and Technology
2013	Academia Europaea
2016	Foreign Member, Russian Academy of Sciences

OTHER:

Co-chairman, Skolkovo Scientific Advisory Council
Chief Academic Counsel, the Minerva Project
Editor-in-Chief, the Annual Review of Biochemistry
Scientific Advisory Boards of the Welch Foundation, Tang Prize Foundation, PrizeForLife
Chief Scientist, Cocrystal Pharma
Executive CEO, InterX
Chairman of Board of Directors: Sensor Kinesis, Cognos
Chairman of Scientific Advisory Board: Protalix, ChromaDex
Director of InterX, Xenetic Biosciences
Professor at the Hebrew University, ShanghaiTech University. Konkuk University

PUBLICATIONS:

1. Berg, P., Kornberg, R.D., Fancher, H., and Dieckmann, M. (1965) Competition between RNA polymerase and DNA polymerase for the DNA template. **Biochem. Biophys. Res. Comm. 18**:243-248.

2. Jackson, J.F., Kornberg, R.D., Berg. P., RajBhandary, U.L, Stuart, A., Khorana, H.G., and Kornberg, A. (1965) On the heterogeneity of the deoxyribonucleic acid associated with crystalline yeast cytochrome b_2. **Biochim. Biophys. Acta 108**:243-248.

3. Kornberg, R.D., and McConnell, H.M. (1971) Inside-outside transitions of phospholipids in vesicle membranes. **Biochemistry 10**:1111-1120.

4. Kornberg, R.D., and McConnell, H.M. (1971) Lateral diffusion of phospholipids in a vesicle membrane. **Proc. Natl. Acad. Sci. USA 68**:2564-2568. PMCID: PMC389469

5. Kornberg, R.D., McNamee, M.G., and McConnell, H.M. (1972) Measurement of transmembrane potentials in phospholipid vesicles. **Proc. Natl. Acad. Sci. USA 69**: 1508-1513. PMCID: PMC426737

6. Kornberg, R.D. (1973) The diffusion of phospholipids in membranes. In **Dynamic Aspects of Conformation Changes in Biological Macromolecules**, C. Sadron, editor, pp. 477-486.

7. Kornberg, R.D., and Thomas, J.O. (1974) Chromatin structure: Oligomers of the histones. **Science 184**:865-868.

8. Kornberg, R.D. (1974) Chromatin structure: A repeating unit of histones and DNA. **Science 184**:868-871.

9. Kornberg, R.D. (1975) A model of chromatin structure. In **The Eukaryote Chromosome**, W. J. Peacock and R.D. Brock, editors. ANU Press (Canberra), pp. 245-253.

10. Noll, M., Thomas, J.O., and Kornberg, R.D. (1975) Preparation of native chromatin and damage caused by shearing. **Science 187**:1203-1206.

11. Thomas, J.O., and Kornberg, R.D. (1975) An octamer of histones in chromatin and free in solution. **Proc. Natl. Acad. Sci. USA 72**:2626-2630. PMCID: PMC432822

12. Finch, J.T., Noll, M., and Kornberg, R.D. (1975) Electron microscopy of defined lengths of chromatin. **Proc. Natl. Acad. Sci. USA 72**:3320-3322. PMCID: PMC432983

13. Thomas, J.O., and Kornberg, R.D. (1975) Cleavable cross-links in the analysis of histone-histone associations. **FEBS Letters 58**:353-358.

14. Kornberg, R.D. (1975) Structure of chromatin. **FEBS Symposia 38**:73.

15. Harrison, S.C., and Kornberg, R.D. (1976) X-Ray diffraction from isolated repeat units of chromatin. In **Molecular Mechanisms in the Control of Gene Expression**. Academic Press Inc., pp. 7-11.

16. Kornberg, R.D. (1977) Structure of chromatin. In **The Molecular Biology of the Mammalian Genetic Apparatus**, P.O.P. T'so, editor, Elsevier (North Holland, Amsterdam), pp. 195-198.

17. Noll, M., and Kornberg, R.D. (1977) Action of micrococcal nuclease on chromatin and the location of H1. **J. Mol. Biol. 109**:393-404.

18. Kornberg, R.D. (1977) Structure of chromatin. **Ann. Rev. Biochem. 46**:931-954.

19. Thomas, J.O., and Kornberg, R.D. (1978) The study of histone-histone associations by chemical cross-linking. **Meth. Cell Biol. 18**:429-440.

20. Prunell, A., and Kornberg, R.D. (1978) Relation of nucleosomes to nucleotide sequences in the rat. **Phil. Trans. R. Soc. Lond. B. 283**:269-173.

21. Prunell, A., and Kornberg, R.D. (1978) Relation of nucleosomes to DNA sequences. **Cold Spring Harbor Symp. Quant. Biol. 42**:103-108.

22. Baer, B.W., and Kornberg, R.D. (1979) Random locations of nucleosomes on genes for 5S rRNA. **J. Biol. Chem. 254**:9678-9681.

23. Prunell, A., Kornberg, R.D., Lutter, L., Klug, A., Levitt, M., and Crick, F.H.C. (1979) Periodicity or deoxyribonuclease I digestion of chromatin. **Science 204**:855-858.

24. Baer, B.W., and Kornberg, R.D. (1980) Repeating structure of cytoplasmic poly(A)-ribonucleoprotein. **Proc. Natl. Acad. Sci. 77**:1890-1892. PMCID: PMC348614

25. Kornberg, R.D., and Klug, A. (1981) The nucleosome. **Scientific American 244**:52-64.

26. Kornberg, R.D. (1981) The location of nucleosomes in chromatin: Specific or statistical? **Nature 292**:579-580.

27. Prunell, A., and Kornberg, R.D. (1982) Variable center-to-center distance of nucleosomes in chromatin. **J. Mol. Biol. 154**:515-523.

28. Baer, B.W., and Kornberg, R.D. (1983) The protein responsible for the repeating structure of cytoplasmic poly(A)-RNP. **J. Cell Biol. 96**:717-721.

29. Uzgiris, E.E., and Kornberg, R.D. (1983) Two-dimensional crystallization technique for imaging macromolecules, with an application to antigen-antibody-complement complexes. **Nature 301**:125-129.

30. Nojima, H., and Kornberg, R.D. (1983) Genes and pseudogenes for mouse U1 and U2 small nuclear RNAs. **J. Biol. Chem. 258**:8151-8155.

31. Bram, R.J., and Kornberg, R.D. (1985) Specific protein binding to far upstream activating sequences in polymerase II promoters. **Proc. Natl. Acad. Sci. USA 82**:43-47. PMCID: PMC396967

32. Sperling, R., Sperling, J., Levine, A.D., Spann, P., Stark, G.R., and Kornberg, R.D. (1985) Abundant nuclear ribonucleoprotein form of CAD RNA. **Mol. Cell. Biol. 5**:569-575. PMCID: PMC366750

33. Sachs, A.B., and Kornberg, R.D. (1985) Nuclear polyadenylate-binding protein. **Mol. Cell. Biol. 5**:1993-1996. PMCID: PMC366917

34. Sachs, A.B., and Kornberg, R.D. (1985) Nuclear poly(A)-binding proteins: Purification and evolutionary conservation. In **Nuclear Envelope Structure and RNA Maturation,** E.A. Smuckler and G.A., Clawson, editors. Alan R. Liss, Inc. (New York, New York), pp. 119-123.

35. Lorch, Y., and Kornberg, R.D. (1985) A region flanking the GAL7 gene and a binding site for GAL4 protein as upstream activating sequences in yeast. **J. Mol. Biol. 186**:821-824. .

36. Bram, R.J., Lue, N.F., and Kornberg, R.D. (1986) A GAL family of upstream activating sequences in yeast: Roles in both induction and repression of transcription. **EMBO J. 5**:603-608. PMCID: PMC1166805

37. Reidler, J., Uzgiris, E.E., and Kornberg, R.D. (1986) Two-dimensional crystals of immunoglobulins. In **Handbook of Experimental Immunology**, 4th Edition, Weir and Herzenberg, editors. Blackwell Scientific Publications (Oxford), pp. 17.1-17.5.

38. Kornberg, R.D. (1986) Overview: Mammalian cell membrane antigens. In **Handbook of Experimental Immunology**, 4th Edition, Weir and Herzenberg, editors. Blackwell Scientific Publications (Oxford), pp. 19.1-19.2.

39. Sachs, A.B., Bond, M.W., and Kornberg, R.D. (1986) A single gene from yeast for both nuclear and cytoplasmic polyadenylate-binding proteins: Domain structure and expression. **Cell 45**:827-835.

40. Rothman, J.E., and Kornberg, R.D. (1986) An unfolding story of protein translocation. **Nature 322**:209-210.

41. Goldfarb, D.S., Gariepi, J., Schoolnik, G., and Kornberg, R.D. (1986) Synthetic peptides as nuclear localization signals, and anti-peptide antibodies for signal recognition. **Nature 322**:641-644.

42. Ludwig, D.S., Ribi, H.O., Schoolnik, G.K., and Kornberg, R.D. (1986) Two-dimensional crystals of cholera toxin B subunit-receptor complexes: Projected structure at 17Å resolution. **Proc. Natl. Acad. Sci. USA 83**:8585-8588. PMCID: PMC386975

43. Bram, R.J., and Kornberg, R.D. (1987) Isolation of a Saccharomyces cerevisiae centromere DNA-binding protein, its human homolog, and its possible role as a transcription factor. **Mol. Cell. Biol.** 7:403-409. PMCID: PMC365082

44. Lorch, Y., LaPointe, J.W., and Kornberg, R.D. (1987) Nucleosomes inhibit the initiation of transcription but allow chain elongation with the displacement of histones. **Cell 49**:203-210.

45. Sachs, A.B., Davis, R.W., and Kornberg, R.D. (1987) A single domain of yeast poly(A)-binding protein is necessary and sufficient for RNA-binding and cell viability. **Mol. Cell. Biol.** 7:3268-3276. PMCID: PMC367964

46. Ribi, H.O., Reichard, P., and Kornberg, R.D. (1987) Two-dimensional crystals of enzyme-effector complexes: ribonucleotide reductase at 18Å resolution. **Biochemistry 26**:7974-7979.

47. Lue, N.F., Chasman, D.I., Buchman, A.R., and Kornberg, R.D. (1987) Interaction of GAL4 and GAL80 regulatory proteins in vitro. **Mol. Cell. Biol.** 7:3446-3451. PMCID: PMC367995

48. Kornberg, R.D., and Ribi, H.O. (1987) Formation of two-dimensional crystals of proteins on lipid layers. In **Protein Structure, Folding, and Design 2**, D.L. Oxender, editor. Alan R. Liss, Inc. (New York, New York), pp. 175-186.

49. Lue, N.F., and Kornberg, R.D. (1987) Accurate initiation at RNA polymerase II promoters in extracts from Saccharomyces cerevisiae. **Proc. Natl. Acad. Sci. USA 84**:8839-8843. PMCID: PMC299646

50. Buchman, A.R., Kimmerly, W.J., Rine, J., and Kornberg, R.D. (1988) Two DNA binding factors recognize specific sequences at silencers, upstream activating sequences, autonomously replicating sequences, and telomeres in Saccharomyces cerevisiae. **Mol. Cell. Biol. 8**:210-225. PMCID: PMC365610. PMCID: PMC363104

51. Ribi, H.O., Ludwig, D.S., Mercer, K.L., Schoolnik, G.K., and Kornberg, R.D. (1988) Three-dimensional structure of cholera toxin penetrating a lipid membrane. **Science 239**:1272-1276.

52. Kimmerly, W., Buchman, A., Kornberg, R., and Rine, J. (1988) Roles of two DNA-binding factors in replication, segregating, and transcriptional repression mediated by a yeast silencer. **EMBO J.** 7:2241-2253.

53. Kornberg, R.D., and Stryer, L. (1988) Statistical distributions of nucleosomes: Nonrandom locations by a stochastic mechanism. **Nucl. Acids Res. 16**:6677-6690. PMCID: PMC338322

54. Lorch, Y., LaPointe, J.W., and Kornberg, R.D. (1988) Nucleosomes and transcription. In **Architecture of Eukaryotic Genes**, G. Kahl, editor. VCH Publishers (Federal Republic of Germany,), pp. 243-249.

55. Darst, S.A., Ribi, H.O., Pierce, D.W., and Kornberg, R.D. (1988) Two-dimensional crystals of Escherichia coli RNA polymerase holoenzyme on positively charged lipid layers. **J. Mol. Biol. 203**:269-273.

56. Fedor, M.J., Lue, N.F., and Kornberg, R.D. (1988) Statistical positioning of nucleosomes by specific protein-binding to an upstream activating sequence in yeast. **J. Mol. Biol. 204**: 109-128.

57. Buchman, A.R., Lue, N.F., and Kornberg, R.D. (1988) Connections between transcriptional activators, silencers, and telomeres as revealed by functional analysis of a yeast DNA-binding protein. **Mol. Cell. Biol. 8**:5086-5099. PMCID: PMC365610

58. Lorch, Y., LaPointe, J.W., and Kornberg, R.D. (1988) On the displacement of histones from DNA by transcription. **Cell 55**:743-744.

59. Lue, N.F., Buchman, A.R., and Kornberg, R.D. (1989) Activation of yeast RNA polymerase II transcription by a thymidine-rich upstream element in vitro. **Proc. Natl. Acad. Sci. USA 86**:486-490. PMCID: PMC286495

60. Fedor, M.J., and Kornberg, R.D. (1989) Upstream activation sequence-dependent alterations of chromatin structure and transcription activation of the yeast GAL1-GAL10 genes. **Mol. Cell. Biol. 9**: 1721-1732. PMCID: PMC362591

61. Kornberg, R.D., LaPointe, J.W., and Lorch, Y. (1989) Preparation of nucleosomes and chromatin. **Methods in Enzymology 170**:3-14.

62. Darst, S.A., Kubalek, E.W., and Kornberg, R.D. (1989) Three-dimensional structure of Escherichia coli RNA polymerase holoenzyme determined by electron crystallography. **Nature 340**: 730-732.

63. Chasman, D.I., Leatherwood, J., Carey, M., Ptashne, M., and Kornberg, R.D. (1989) Activation of yeast polymerase II transcription by herpesvirus VP16 and GAL4 derivatives in vitro. **Mol. Cell. Biol. 9**: 4746-4749. PMCID: PMC363622

64. Lue, N.F., Flanagan, P., Sugimoto, K., and Kornberg, R.D. (1989) Initiation by yeast RNA polymerase II at the adenoviral major late promoter in vitro. **Science 246**:661-664.

65. Kornberg, R.D., Buchman, A.R., Chasman, D.I., Darst, S.A., Edwards, A.M., Feaver, W.J., Flanagan, P.M., Kelleher, R.J., Kubalek, E.W., LaPointe, J.W., Lorch, Y., and Lue, N.F. (1989) Gene

activation and transcription with purified factors from yeast. In **Gene Regulation and AIDS**, T.S. Papas, editor. Gulf Publishing Co. (Houston, Texas), pp. 9-18.

66. Buchman, A.R., and Kornberg, R.D. (1990) A yeast ARS-binding protein activates transcription synergistically in combination with other weak activating factors. **Mol. Cell. Biol. 10**:887-897. PMCID: PMC360926

67. Edwards, A.M., Darst, S.A., Feaver, W.J., Thompson, N.E., Burgess, R.R., and Kornberg, R.D. (1990) Purification and lipid layer crystallization of yeast RNA polymerase II. **Proc. Natl. Acad. Sci. USA 87**:2122-2126. PMCID: PMC53638

68. Chasman, D.I., Lue, N.F., Buchman, A.R., LaPointe, J.W., Lorch, Y., and Kornberg, R.D. (1990) A yeast protein that influences the chromatin structure of UAS_G and functions as a powerful auxiliary gene activator. **Genes & Development 4**:503-514.

69. Chasman, D.I., and Kornberg, R.D. (1990) GAL4 protein: Purification, association with GAL80 protein, and conserved domain structure. **Mol. Cell. Biol. 10**:2916-2923. PMCID: PMC360654

70. Sachs, A.B., and Kornberg, R.D. (1990) Purification and characterization of polyadenylate-binding protein. **Methods in Enzymology 181**:332-352.

71. Kelleher, III, R.J., Flanagan, P.M., and Kornberg, R.D. (1990) A novel mediator between activator proteins and the RNA polymerase II transcription apparatus. **Cell 61**:1209-1215.

72. Flanagan, P.M., Kelleher, III, R.J., Feaver, W.J., Lue, N.F., LaPointe, J.W., and Kornberg, R.D. (1990) Resolution of factors required for the initiation of transcription by yeast RNA polymerase II. **J. Biol. Chem. 265**:11105-11107.

73. Kornberg, R.D., Buchman, A.R., Chasman, D.I., Darst, S.A., Edwards, A., Flanagan, P., Kelleher, R., Lorch, Y., Lue, N.F., and Sugimoto, K. (1990) Gene activation and transcription in a soluble system from yeast. In **Developmental Biology**, E.H. Davidson, J.V. Ruderman, J.W. Posakony, editors. Wiley-Liss, Inc. (New York, New York), pp. 307-317.

74. Lue, N.F., and Kornberg, R.D. (1990) Accurately initiated, enhancer-dependent transcription by RNA polymerase I in yeast extracts. **J. Biol. Chem. 265**:18091-18094.

75. Lorch, Y., Lue, N.F., and Kornberg, R.D. (1990) Interchangeable RNA polymerase I and II enhancers. **Proc. Natl. Acad. Sci. USA 87**:8202-8206. PMCID: PMC54923

76. Schultz, P., Celia, H., Riva, M., Darst, S.A., Colin, P., Kornberg, R.D., Sentenac, A., and Oudet, P. (1990) Structural study of the yeast RNA polymerase A: Electron microscopy of lipid-bound molecules and two-dimensional crystals. **J. Mol. Biol. 216**:353-362.

77. Lue, N.F., Flanagan, P.M., Kelleher, III, R.J., Edwards, A.M., and Kornberg, R.D. (1990) RNA polymerase II transcription in vitro. **Methods in Enzymology 194**:545-550.

78. Edwards, A.M., Kane, C.M., Young, R.A., and Kornberg, R.D. (1991) Two dissociable subunits of yeast RNA polymerase II stimulate the initiation of transcription at a promoter in vitro. **J. Biol. Chem. 266**:71-75.

79. Darst, S.A., Ahlers, M., Meller, P.H., Kubalek, E.W., Blankenburg, R., Ribi, H.O., Ringsdorf, H., and Kornberg, R.D. (1991) Two-dimensional crystals of streptavidin on biotinylated lipid layers and their interactions with biotinylated macromolecules. **Biophysical J. 59**:387-396. PMCID: PMC1281155

80. Kubalek, E.W., Kornberg, R.D., and Darst, S.A. (1991) Improved transfer of two-dimensional crystals from the air/water interface to specimen support grids for high-resolution analysis by electron microscopy. **Ultramicroscopy 35**:295-304.

81. Flanagan, P.M., Kelleher III, R.J., Sayre, M.H., Tschochner, H., and Kornberg, R.D. (1991). A mediator for activation of RNA polymerase II transcription in vitro. **Nature 350**:436-438.

82. Darst, S.A., Edwards, A.M., Kubalek, E.W., and Kornberg, R.D. (1991) Three-dimensional structure of yeast RNA polymerase II at 16Å resolution. **Cell 66**:121-128.

83. Kornberg, R.D., and Darst, S.A. (1991) Two-dimensional crystals of proteins on lipid layers. **Current Opinion in Structural Biology 1**:642-646.

84. Darst, S.A., Kubalek, E.W., Edwards, A.M., and Kornberg, R.D. (1991) Two-dimensional and epitaxial crystallization of a mutant form of yeast RNA polymerase II. **J. Mol. Biol. 221**:347-357.

85. Feaver, W.J., Gileadi, O., and Kornberg, R.D. (1991) Purification and characterization of yeast RNA polymerase II transcription factor b. **J. Biol. Chem. 266**:19000-19005.

86. Kornberg, R.D., and Lorch, Y. (1991) Irresistible force meets immovable object: Transcription and the nucleosome. **Cell 67**:833-836.

87. Feaver, W.J., Gileadi, O., Li, Y., and Kornberg, R.D. (1991) CTD kinase associated with yeast RNA polymerase II initiation factor b. **Cell 67**:1223-1330.

88. Kornberg, R.D., Chasman, D.I., Darst, S.A., Edwards, A.M., Feaver, W.J., Flanagan, P.M., Gileadi, O., Henry, N.L., Kelleher III, Li, Y., R.J., Lorch, Y., Lue, N.F., Sayre, M.H., and Tschochner, H. (1992) Yeast RNA polymerase II transcription in vitro: General initiation factors; novel mediator of transcriptional activation; three-dimensional structure of RNA polymerase II. In **Transcriptional Regulation**, pp. 349-362, Cold Spring Harbor Press.

89. Kelleher III, R.J., Flanagan, P.M., Chasman, D.I., Ponticelli, A.S., Struhl, K., and Kornberg, R.D. (1992) Yeast and human TFIIDs are interchangeable for the response to acidic transcriptional activators in vitro. **Genes & Development 6**:296-303.

90. Cairns, B.R., Ramer, S.W., and Kornberg, R.D. (1992) Order of action of components in the yeast pheromone response pathway revealed with a dominant allele of the STE11 kinase and the multiple phosphorylation of the STE7 kinase. **Genes & Development 6**:1305-1318.

91. Kornberg, R.D., and Lorch, Y. (1992) Chromatin structure and transcription. **Annu. Rev. Cell Biol. 8**:563-589.

92. Gileadi, O., Feaver, W.J., and Kornberg, R.D. (1992) Cloning of a subunit of yeast RNA polymerase II transcription factor b and CTD kinase. **Science 257**:1389-1392.

93. Flanagan, P.M., Kelleher III, R.J., Tschochner, H., Sayre, M.H., and Kornberg, R.D. (1992) Simple derivation of TFIID-dependent RNA polymerase II transcription systems from Schizosaccharomyces pombe and other organisms, and factors required for transcriptional activation. **Proc. Natl. Acad. Sci. USA 89**:7659-7663. PMCID: PMC49770

94. Ku, A.C., Darst, S.A., Kornberg, R.D., Robertson, C.R., and Gast, A.P. (1992) Dendritic growth of two-dimensional protein crystals. **Langmuir 8**:2357-2360.

95. Sayre, M.H., Tschochner, H., and Kornberg, R.D. (1992) Reconstitution of transcription with five purified protein factors and RNA Polymerase II from Saccharomyces cerevisiae. **J. Biol. Chem. 267**:23376-23382.

96. Sayre, M.H., Tschochner, H., and Kornberg, R.D. (1992) Purification and properties of Saccharomyces cerevisiae RNA polymerase II general initiation factor a. J. Biol. Chem. 267:23383-23387.

97. Henry, N.L., Sayre, M.H., and Kornberg, R.D. (1992) Purification and characterization of yeast RNA polymerase II general initiation factor g. J. Biol. Chem. 267:23388-23392.

98. Tschochner, H., Sayre, M.H., Flanagan, P.M., Feaver, W.J., and Kornberg, R.D. (1992) Yeast RNA polymerase II initiation factor e: Isolation and identification as the functional counterpart of human transcription factor IIB. **Proc. Natl. Acad. Sci. USA. 89**:11291-11296. PMCID: PMC50536

99. Lorch, Y., LaPointe, J.W., and Kornberg, R.D. (1992) Initiation on chromatin templates in a yeast RNA polymerase II transcription system. **Genes & Development 6**:2282-2287.

100. Ku, A.C., Darst, S.A., Robertson, C.R., Gast, A.P., and Kornberg, R.D. (1993) Molecular analysis of two-dimensional protein crystallization. **J. Physical Chemistry 97**:3013-3016.

101. Lorch, Y., and Kornberg, R.D. (1993) Near zero linking difference upon TFIID binding to promoter DNA. **Mol. Cell. Biol. 13**:1872-1875. PMCID: PMC359500

102. Lorch, Y., and Kornberg, R.D. (1993) Nucleosome positioning. **Nucleic Acids and Molecular Biology** 7:217-225.

103. Lue, N.F., and Kornberg, R.D. (1993) A possible role for the yeast TATA-element binding protein in DNA replication. **Proc. Natl. Acad. Sci. USA 90**:8018-8022. PMCID: PMC47279

104. Chasman, D.I., Flaherty, K.M., Sharp, P.A., and Kornberg, R.D. (1993) Crystal structure of yeast TATA-binding protein and model for interaction with DNA. **Proc. Natl. Acad. Sci. USA 90**:8174-8178. PMCID: PMC47311

105. Sayre, M.H., and Kornberg, R.D. (1993) Mechanism and regulation of yeast RNA polymerase II transcription. **Cellular and Molecular Biology Research 39**:349-354.

106. Feaver, W.J., Svejstrup, J.Q., Bardwell, L., Bardwell, A.J., Buratowski, S., Gulyas, K.D., Donahue, T.F., Friedberg, E.C., and Kornberg, R.D. (1993) Dual roles of a multiprotein complex from S. cerevisiae in transcription and DNA repair. **Cell 75**:1379-1387.

107. Kornberg, R.D., Bushnell, D., Edwards, A.M., Feaver, W.J., Flanagan, P.M., Gileadi, O., Henry N.L., Kelleher III, R.J., Li, Y., Lorch, Y., Lue, N.F., Sayre, M.H., Svejstrup, J., and Tschochner, H. (1994) Resolution and reconstruction of yeast RNA polymerase II transcription. In **Transcription: Mechanisms and Regulation**, R.C. Conaway and J.W. Conaway, editors. Raven Press, Ltd. (New York, New York) pp. 19-26.

108. Li, Y., Flanagan, P.M., Tschochner, H., and Kornberg, R.D. (1994) RNA polymerase II initiation factor interactions and transcription start site selection. **Science 263**:805-807.

109. Cairns, B.R., Kim, Y.J., Sayre, M.H., Laurent, B.C., and Kornberg, R.D. (1994) A multisubunit complex containing the SWI1/ADR6, SWI2/SNF2, SWI3, SNF5, and SNF6 gene products isolated from yeast. **Proc. Natl. Acad. Sci. USA 91**:1950-1954. PMCID: PMC43282

110. Wang, Z., Svejstrup, J.Q., Feaver, W.J., Wu, X., Kornberg, R.D., and Friedberg, E.C. (1994) Transcription factor b (TFIIH) is required during nucleotide-excision repair in the yeast. **Nature 368**:74-76.

111. Li, Y., and Kornberg, R.D. (1994) Interplay of positive and negative effectors in function of the C-terminal repeat domain of RNA polymerase II. **Proc. Natl. Acad. Sci. USA 91**:2362-2366. PMCID: PMC43371

112. Edwards, A.M., Darst, S.A., Hemming, S.A., Li, Y., and Kornberg, R.D. (1994) Epitaxial growth of protein crystals on lipid layers. **Nature Structural Biology 1**:195-197.

113. Bardwell, L., Bardwell, A.J., Feaver, W.J., Svejstrup, J., Kornberg, R.D., and Friedberg, E.C. (1994) Yeast RAD3 protein binds directly to both SSL2 and SSL1 proteins: Implications for the structure and function of transcription/ repair factor b. **Proc. Natl. Acad. Sci. USA 91**:3926-3930. PMCID: PMC43695

114. Kim, T.K., Hashimoto, S., Kelleher III, R.J., Flanagan, P.M., Kornberg, R.D., Horikoshi, M., and Roeder, R.G. (1994) Effects of activation-defective TBP mutations on transcription initiation in yeast. **Nature 369**:252-255.

115. Kim, Y.J., Bjorklund, S., Li, Y., Sayre, M.H., and Kornberg, R.D. (1994) A multiprotein mediator of transcriptional activation and its interaction with the C-terminal repeat domain of RNA polymerase II. **Cell 77**:599-608.

116. Bardwell, A.J., Bardwell L., Iyer, N., Svejstrup, J.Q., Feaver, W.J., Kornberg, R.D., and Friedberg, E.C. (1994) Yeast nucleotide excision repair proteins Rad2 and Rad4 interact with RNA polymerase II basal transcription factor b. **Mol. Cell. Biol. 14**:3569-3576. PMCID: PMC358724

117. Henry, N.L., Campbell, A.M., Feaver, W.J., Poon, D., Weil, P.A., and Kornberg, R.D. (1994) TFIIF-TAF-RNA polymerase II connection. **Genes and Development 8**:2868-2878.

118. Feaver, W.J., Henry, N.L., Bushnell, D.A., Sayre, M.H., Brickner, J.H., Gileadi, O., and Kornberg, R.D. (1994) Yeast TFIIE: Cloning, expression and homology to vertebrate proteins. **J. Biol. Chem. 269**:27549-27553.

119. Lorch, Y., and Kornberg, R.D. (1994) Isolation of the yeast histone octamer. **Proc. Natl. Acad. Sci. USA 91**:11032-11034. PMCID: PMC45160

120. Svejstrup, J.Q., Feaver, W.J., LaPointe, J., and Kornberg, R.D. (1994) RNA polymerase transcription factor IIH holoenzyme from yeast. **J. Biol. Chem. 269**:28044-28048.

121. Feaver, W.J., Svejstrup, J.Q., Henry, N.L., and Kornberg, R.D. (1994) Relationship of CDK-activating kinase and RNA polymerase II CTD kinase TFIIH/TFIIK. **Cell 79**:1103-1109.

122. Svejstrup, J.Q., Wang, Z., Feaver, W.J., Wu, X., Bushnell, D.A., Donahue, T.F., Friedberg, E.C., and Kornberg, R.D. (1995) Different forms of TFIIH for transcription and DNA repair: Holo-TFIIH and a nucleotide excision repairosome. **Cell 80**:21-28. .

123. Friedberg, E.C., Bardwell, A.J., Bardwell, L., Feaver, W.J., Kornberg, R.D., Svejstrup, J.Q., Tomkinson, A.E., and Wang, Z. (1995) Nucleotide excision repair in the yeast Saccharomyces cerevisiae:: Its relationship to specialized mitotic recombination and RNA polymerase II basal transcription. **Phil. Trans. Royal Soc. London B 347**:63-68.

124. Hemming, S.A., Bochkarev, A., Darst, S.A., Kornberg, R.D., Ala, P., Yang, D.S.C., and Edwards, A.M. (1995) The mechanism of protein crystal growth from lipid layers. **J. Mol. Biol. 246**:308-316.

125. Asturias, F.J., and Kornberg, R.D. (1995) A novel method for transfer of two-dimensional crystals from the air/water interface to specimen grids. **J. Structural Biology 114**:60-66. :

126. Wang, Z., Buratowski, S., Svejstrup, J.Q., Feaver, W.J., Wu, X., Kornberg, R., Donahue, T.F., and Friedberg, E.C. (1995) Yeast TB1 and SSL1 genes, which encode subunits of transcription factor IIH (TFIIH), are required for nucleotide excision repair and RNA polymerase II transcription. **Mol Cell. Biol. 15**:2288-2293. PMCID: PMC230456

127. Kornberg, R.D., and Lorch, Y. (1995) Interplay between chromatin structure and transcription. **Current Opinion in Cell Biology** 7:371-375.

128. Poon, D., Bai, Y., Campbell, A.M., Bjorkland, S., Kim. Y.-J., Zhou, S., Kornberg, R.D., and Weil, P.A. (1995) Identification and characterization of a TFIID-like multiprotein complex from Sacchararomyces cerevisiae. **Proc. Natl. Acad. Sci. USA 92**:8224-8228. PMCID: PMC41129

129. Li, Y., Bjorklund, S., Jiang, Y.W., Kim, Y.-J., Lane, W.S., Stillman, D.J., and Kornberg, R.D. (1995) Yeast global transcriptional regulators Sin4 and Rgr1 are components of mediator complex/RNA polymerase II holoenzyme. **Proc. Natl. Acad. Sci. USA 92**:10864-10868. PMCID: PMC40531

130. Sugimoto, K., Matsumoto, K., Kornberg, R.D., Reed, S.I., and Wittenberg, C. (1995) Dosage suppressors of a dominant G1 cyclin mutant, CLN3-2: Identification of a yeast gene encoding a putative RNA/ssDNA binding protein. **Mol. Gen. Genet. 248**:712-718.

131. Svejstrup, J.Q., Feaver, W.J., and Kornberg, R.D. (1996) Subunits of yeast RNA polymerase II transcription factor TFIIH encoded by the CCL1 gene. **J. Biol. Chem. 271**:643-645.

132. Li, Y., Bjorklund, S., Kim, Y.-J., and Kornberg, R.D. (1996) Yeast RNA polymerase II holoenzyme. **Methods in Enzymology 273**:172-176.

133. Meredith, G.D., Chang, W.-H., Li, Y., Bushnell, D.A., Darst, S.A., and Kornberg, R.D. (1996) The C-terminal domain in the structure of RNA polymerase II. **J. Mol. Biol. 258**:413-419.

134. Leuther, K.K., Bushnell, D.A., and Kornberg, R.D. (1996) Two-dimensional crystallography of transcription factor IIB- and IIE-RNA polymerase II complexes: Implications for start site selection and initiation complex formation. **Cell 85**:773-779.

135. Cairns, B.R., Henry, N.L., and Kornberg, R.D. (1996) TFG3/TAF30/ANC1, a component of the yeast SWI/.SNF complex that is similar to the leukemogenic proteins ENL and AF-9. **Mol. Cell. Biol. 16**:3308-3316.

136. Kornberg, R.D. (1996) The nucleosome. In **Principles of Medical Biology 5, Molecular and Cellular Genetics**, pages 1-10. E.E. Bittar and N. Bittar, editors, JAI Press Ltd. (London).

137. Bushnell, D.A., Bamdad, C., and Kornberg, R.D. (1996) A minimal set of RNA polymerase II transcription protein interactions. **J. Biol. Chem. 271**:20170-20174.

138. Henry, N.L., Bushnell, D.A., and Kornberg, R.D. (1996) A yeast transcriptional stimulatory protein similar to human PC4. **J. Biol. Chem. 271**:21842-21847. .

139. Cairns, B.R., Levinson, R.S., Yamamoto, K.R., and Kornberg, R.D. (1996) Essential role of Swp73p in function of the yeast Swi/Snf complex. **Genes & Development 10**:2131-2144. PMCID: PMC231325

140. Sakurai, H., Kim, Y.-J., Ohishi, T., Kornberg, R.D., and Fukasawa, T. (1996) The yeast GAL11 protein binds to the transcription factor IIE through GAL11 regions essential for its in vivo function. **Proc. Natl. Acad. Sci. USA 93**:9488-9492. PMCID: PMC38455

141. Kornberg, R.D. (1996) RNA polymerase II transcription control. **TIBS 21**:325-326.

142. Cairns, B.R., Lorch, Y., Li, Y., Zhang, M., Lacomis, L., Erdjument-Bromage, H., Tempst, P., Laurent, B., Kornberg, R.D. (1996) RSC, an essential, abundant chromatin-remodeling complex. **Cell 87**:1249-1260.

143. Gustafsson, C.M., Myers, L.C., Li, Y., Redd, M.J., Erdjument-Bromage, H., Tempst, P., and Kornberg, R.D. (1997) Identification of Rox3 as a component of mediator and RNA polymerase II holoenzyme. **J. Biol. Chem. 272**:48-50.

144. Wang, Z., Wei, S., Reed, S.H., Wu, X, Svejstrup, J.Q., Feaver, W.J., Kornberg, R.D., and Friedberg, E.C. (1997) The RAD7, RAD16 and RAD23 genes of Saccharomyces cerevisiae: Requirement for transcription-independent nucleotide excision repair in vitro and interactions between the gene products. **Mol. Cell. Biol. 17**:635-643. PMCID: PMC231789

145. Cao, Y., Cairns, B.R., Kornberg, R.D., and Laurent, B.C. (1997) Sfh1p, a component of a novel chromatin-remodeling complex, is required for cell cycle progression. **Mol. Cell. Biol. 17**:3323-3334. PMCID: PMC232185

146. Svejstrup, J.Q., Li, Y., Fellows, J., Gnatt, A., Bjorklund S., and Kornberg, R.D. (1997) Evidence for a mediator cycle at the initiation of transcription. **Proc. Natl. Acad. Sci. USA 94**:6075-6078. PMCID: PMC21003

147. Myers, L., Leuther, K., Bushnell, D.A., Gustafsson, C., and Kornberg R.D. (1997) Yeast RNA polymerase II transcription reconstituted with purified proteins. **METHODS: A Companion to Methods in Enzymology 12**:212-216.

148. Feaver, W.J., Henry, N.L., Wang, Z., Wu, X., Svejstrup, J.Q., Bushnell, D.A., Friedberg, E., and Kornberg R.D. (1997) Genes for Tfb2, Tfb3, and Tfb4 subunits of yeast transcription/repair factor IIH: Homology to human cyclin-dependent kinase activating kinase and IIH subunits. **J. Biol. Chem. 272:19319**-19327.

149. Asturias, F.J., Meredith, G.D., Poglitsch, C.L., and Kornberg, R.D. (1997) Two conformations of RNA polymerase II revealed by electron crystallography. **J. Mol. Biol. 272**:536-540.

150. Gnatt, A., Fu, J., and Kornberg, R.D. (1997) Formation and crystallization of yeast RNA polymerase II elongation complexes. **J. Biol. Chem. 272**:30799-30805.

151. Edwards, A.M., Darst, S.A., Hemming, S.A., Asturias, F.J., David, P.R., and Kornberg, R.D. (1997) Two-dimensional protein crystals in aid of three-dimensional protein crystal growth. **Methods in Enzymology 276**:166-171.

152. Myers, L.C., Gustafsson, C.M., Lui, M., Erdjument-Bromage, H., Tempst, P., and Kornberg, R.D. (1998) The Med proteins of yeast and their function through the RNA polymerase II carboxy-terminal domain. **Genes & Development 12**:45-54. PMCID: PMC316402

153. Asturias, F.J., Chang, W., Li, Y., and Kornberg, R.D. (1998) Electron crystallography of yeast RNA polymerase II preserved in vitreous ice. **Ultramicroscopy 70**:133-144.

154. Fu, J., Gerstein, M., David, P., Gnatt, A.L., Bushnell, D.A., Edwards, A.M., and Kornberg, R.D. (1998) Repeated tertiary fold of RNA polymerase II and implications for DNA binding. **J. Mol. Biol. 280**:317-322.

155. Jensen, G.J., Meredith, G., Bushnell, D.A., and Kornberg, R.D. (1998) Structure of wild type RNA polymerase II. **EMBO J. 17**:2353-2358. PMCID: PMC1170578

156. Jiang, Y.W., Veschambre, P., Erdjument-Bromage, H., Tempst, P., Conaway, J.W., Conaway, R.C., and Kornberg, R.D. (1998) Mammalian mediator of transcriptional regulation and its possible role as an end-point of signal transduction pathways. **Proc. Natl. Acad. Sci. USA 95**:8538-8543. PMCID: PMC21111

157. Jensen, G.J., and Kornberg, R.D. (1998) Single particle selection and alignment with heavy atom cluster-antibody conjugates. **Proc. Natl. Acad. Sci. USA 95**:9262-9267. PMCID: PMC21326

158. Lorch, Y., Cairns, B.R., Zhang, M., and Kornberg, R.D. (1998) Activated RSC-nucleosome complex and persistently altered form of the nucleosome. **Cell 94**:29-34.

159. Gustafsson, C.M., Myers, L.C., Beve, J., Spahr, H., Lui, M., Erdjument-Bromage, H., Tempst, P., and Kornberg, R.D. (1998) Identification of new mediator subunits in the RNA polymerase II holoenzyme from Saccharomyces cerevisiae. **J. Biol. Chem. 273**:30851-30854.

160. Cairns, B.R., Erdjument-Bromage, H., Tempst, P, Winston, F., and Kornberg, R.D. (1998) Two actin-related proteins are shared functional components of the chromatin remodeling complexes RSC and SWI/SNF. **Molecular Cell 2**:639-651.

161. Kornberg, R.D. (1998) Mechanism and regulation of yeast RNA polymerase II transcription. **Cold Spring Harbor Symposium on Quantitative Biology**, Volume LXIII, Cold Spring Harbor Laboratory Press, pp. 229-232.

162. Myers, L.C., Gustafsson, C.M., Hayashibara, K.C., Brown, P.O., and Kornberg, R.D. (1999) Mediator protein mutations that selectively abolish activated transcription. **Proc. Natl. Acad. Sci. USA 96:**67-72. PMCID: PMC15094

163. Lorch, Y., Zhang, M., and Kornberg, R.D. (1999) Histone octamer transfer by a chromatin-remodeling complex. **Cell 96**:389-392.

164. Asturias, F.J., Jiang, Y.W., Myers, L.C., Gustafsson, C.M., and Kornberg, R.D. (1999). Conserved structures of Mediator and RNA Polymerase II holoenzyme. **Science 283**:985-987.

165. Leuther, K.K., Hammarsten, O., Kornberg, R.D., and Chu, G. (1999) Structure of DNA-dependent protein kinase: Implications for its activation by DNA. **EMBO J. 18**:1114-1123. PMCID: PMC1171203

166. Asturias, F.J. and Kornberg, R.D. (1999) Protein crystallization on lipid layers and structure determination of the RNA polymerase II transcription initiation complex. **J. Biol. Chem. 274**:6813-6816.

167. Kornberg, R.D. and Lorch, Y. (1999) Chromatin-modifying and –remodeling complexes. **Current Opinion in Genetics & Development 9**:148-151.

168. Kornberg, R.D. and Lorch Y. (1999) Twenty-five years of the nucleosome, fundamental particle of the eukaryote chromosome. **Cell: 98**:285-294.

169. Poglitsch, C.L., Meredith, G., Gnatt, A., Jensen, G.J., Chang, W-H., Fu, J, and Kornberg, R.D. (1999) Electron crystal structure of an RNA polymerase II transcription elongation complex. **Cell 98**:791-798.

170. Fu, J., Gnatt, A.L., Bushnell, D.A., David, P.R., Jensen, G.J., and Kornberg, R.D. (1999) Yeast RNA polymerase II at 5 Å resolution. **Cell 98**:799-810.

171. Cairns, B.R., Schlichter, A., Erdjument-Bromage, H., Tempst, P., Kornberg, R.D., and Winston, F. (1999) Two functionally distinct forms of the RSC nucleosome-remodeling complex, containing essential AT hook, BAH, and bromodomains. **Molecular Cell 4**:715-723.

172. Kornberg, R.D. (1999) Eukaryotic transcriptional control. TIBS 24:M46-M49 (Millennium Issue).

173. Feaver, W.J., Huang, W., Gileadi, O., Myers, L., Gustafsson, C.M., Kornberg, R.D., and Friedberg, E.C. (2000) Subunit interactions in yeast transcription/repair factor TFIIH. **J. Biol. Chem. 275**:5941-5946.

174. Cramer, P., Bushnell, D.A., Fu, J., Gnatt, A.L., Maier-Davis, B., Thompson, N.E., Burgess, R.R., Edwards, A.M., David, P.R., and Kornberg, R.D. (2000) Architecture of RNA polymerase II and implications for the transcription mechanism. **Science 288**:640-649.

175. Jensen, G.J. and Kornberg, R.D. (2000) Defocus-gradient corrected back-projection. **Ultra-microscopy 84:**57-64.

176. Myers, L.C. and Kornberg, R.D. (2000) Mediator of transcriptional regulation. **Ann. Rev. Biochem. 69**:729-749.

177. Lorch, Y., Beve, J., Gustafsson, C.M., Myers, L.C., and Kornberg, R.D. (2000) Mediator-nucleosome interaction. **Molecular Cell 6:**197-201. .

178. Chang, W.-H. and Kornberg R.D. (2000) Electron crystal structure of the transcription factor and DNA repair complex, core TFIIH. **Cell 102**:609-613.

179. Dotson, M.R., Yuan, C.X., Roeder, R.G., Myers, L.C., Gustafsson, C.M., Jiang, Y.W., Yang, L., Kornberg, R.D. and Asturias, F.J. (2000) Structural organization of yeast and mammalian mediator complexes. **Proc. Natl. Acad. Sci. USA 97**:14307-14310. PMCID: PMC18914

180. Bushnell, D.A., Cramer, P., and Kornberg, R.D. (2001) Selenomethionine incorporation in Saccharomyces cerevisiae RNA polymerase II. **Structure 9**:R11-R14.

181. Lorch, Y., Zhang, M., and Kornberg, R.D. (2001) RSC unravels the nucleosome. **Molecular Cell 7**:89-95.

182. Cramer, P., Bushnell, D.A., and Kornberg, R.D. (2001) Structural basis of transcription: RNA polymerase II at 2.8 Ångstrom resolution. **Science 292:**1863-1876. .

183. Gnatt, A.L., Cramer, P., Fu, J., Bushnell. D.A., and Kornberg, R.D. (2001) Structural basis of transcription: An RNA polymerase II elongation complex at 3.3 Å resolution. **Science 292**:1876-1882.

184. Li, Y., Takagi, Y., Jiang, Y., Tokunaga, Erdjument-Bromage, H., Tempst, P., and Kornberg, R.D. (2001) A multiprotein complex that interacts with RNA polymerase II elongator. **J. Biol. Chem. 276**:29628-29631.

185. Kornberg, R.D. (2001) The eukaryotic gene transcription machinery. **Biol. Chem. 382**:1109-1107.

186. Borggrefe, T., Davis, R., Bareket-Samish, A., and Kornberg, R.D. (2001) Quantitation of the RNA polymerase II transcription machinery in yeast. **J. Biol. Chem. 276**:47150-47153.

187. Nagy, P.L., Griesenbeck, J., Kornberg, R.D., and Cleary, M.L. (2002) A truthorax group complex purified from Saccharomyces cerevisiae is required for methylation of histone H3. **Proc. Natl. Acad. Sci. USA 99**:90-94. PMCID: PMC117519

188. Bushnell, D.A., Cramer, P., and Kornberg, R.D. (2002) Structural basis of transcription: α–Amanitin-RNA polymerase II cocrystal at 2.8 Å resolution. **Proc. Natl. Acad. Sci. USA 99**:1218-1222. PMCID: PMC122170

189. Kornberg, R.D. and Lorch Y. (2002) Chromatin structure and transcription: Where do we go from here? **Current Opinion in Genetics & Development 12**:249-251.

190. Davis, J.A., Takagi, Y. Kornberg, R.D., and Asturias, F.J. (2002) Structure of the yeast RNA polymerase II holoenzyme: conformation and polymerase interaction. **Molecular Cell 10**:409-415.

191. Borggrefe, T., Davis, R., Erdjument-Bromage, H., Tempst, P., and Kornberg, R.D. (2002) A complex of the Srb8, -9, -10, and -11 transcriptional regulatory proteins from yeast. **J. Biol. Chem. 277**:44202-44207.

192. Asturias, F.J., Chung, W.-C., Kornberg, R.D., and Lorch, Y. (2002) Structural analysis of the RSC chromatin-remodeling complex. **Proc. Natl. Acad. Sci. USA 99**:13477-13480. PMCID: PMC129698

193. Boeger, H., Griesenbeck, J., and Kornberg, R.D. (2003) Nucleosomes unfold completely at a transcriptionally active promoter. **Molecular Cell 11**:1587-1598.

194. Bushnell, D.A. and Kornberg, R.D. (2003) Complete, 12-subunit RNA polymerase II at 4.1 Å resolution: Implications for the initiation of transcription. **Proc. Natl. Acad. Sci. USA 100**:6969-6973. PMCID: PMC165814

195. Chung, W.-H., Craighead, J.L., Chang, W.-H., Ezeokonkwo, E., Baraket-Samish, A., Kornberg, R.D., and Asturias, F.J. (2003) RNA polymerase II/TFIIF structure and conserved organization of the initiation complex. **Molecular Cell 12**:1003-1013.

196. Kuras, L., Borggrefe, T., and Kornberg, R.D. (2003) Association of the Mediator complex with enhancers of active genes. **Proc. Natl. Acad. Sci. USA 100**:13887-13891. PMCID: PMC283516

197. Takagi, Y., Komori, H., Chang, W.-H., Hudmon, A., Erdjument-Bromage, H., Tempst, P., and Kornberg, R.D. (2003) Revised subunit structure of yeast TFIIH and reconciliation with human TFIIH. **J. Biol. Chem. 278**:43897-43900. .

198. Griesenbeck, J., Boeger, H., Strattan, J.S., and Kornberg, R.D. (2003) Affinity purification of specific chromatin segments from chromosomal loci in yeast. **Mol. Cell. Biol. 23**:9275-9282.

199. Bushnell, D.A., Westover, K.D., Davis, R., and Kornberg, R.D. (2004) Structural basis of transcription: an RNA polymerase II – TFIIB cocrystal at 4.5 Å. **Science 303**:983-988.

200. Westover, K.D., Bushnell, D.A., and Kornberg, R.D. (2004) Structural basis of transcription: separation of RNA and DNA by RNA polymerase II. **Science 303**:1014-1016.

201. Griesenbeck, J., Boeger, H., Strattan, J.S., and Kornberg. R.D. (2004) Purification of defined chromosomal domains. **Methods in Enzymology 375**:170-178. PMCID: PMC309680

202. Lorch, Y. and Kornberg, R.D. (2004) Isolation and assay of the RSC chromatin-remodeling complex from Saccharomyces cerevisiae. **Methods in Enzymology 377**:316-322.

203. Bourbon, H.M. et al. (2004) A unified nomenclature for protein subunits of Mediator complexes linking transcriptional regulators to RNA polymerase II. **Mol. Cell 14**:553-557.

204. Boeger, H., Griesenbeck, J., Strattan, J.S., and Kornberg, R.D. (2004) Removal of promoter nucleosomes by disassembly rather than sliding in vivo. **Mol. Cell 14**:667-673.

205. Westover, K.D., Bushnell, D.A., and Kornberg, R.D. (2004) Structural basis of transcription: Nucleotide selection by rotation in the RNA polymerase II active center. **Cell 119**:481-489.

206. Batada, N., Westover, K.A., Bushnell, D.A., Levitt, M., and Kornberg, R.D. (2004) Diffusion of nucleoside triphosphates and role of the entry site to the RNA polymerase II active center. **Proc. Natl. Acad. Sci. USA 101**:17361-17364. PMCID: PMC536049

207. Lorch, Y., Maier-Davis, B., and Kornberg, R.D. (2005) Chromatin remodeling by DNA bending, not twisting. **Proc. Natl. Acad. Sci. USA 102**:1329-1332. PMCID: PMC546017

208. Ackerson, C.J., Jadzinsky, P.D., and Kornberg, R.D. (2005) Thiolate ligands for synthesis of water soluble gold clusters. **J. Am. Chem. Soc. 127**:6550-6551.

209. Takagi, Y., Masuda, C.A., Chang, W.-H., Komori, H., Wang, D., Hunter, T., Joazeiro, C.A.P., and Kornberg, R.D. (2005) Ubiquitin ligase activity of TFIIH and the transcriptional response to DNA damage. **Mol. Cell 18**:237-243.

210. Boeger, H., Bushnell, D.A., Davis, R., Griesenbeck, J., Lorch, Y., Strattan, J.S., Westover, K.D., and Kornberg, R.D. (2005) Structural basis of eukaryotic gene transcription. **FEBS Lett. 579:**899-903.

211. Kornberg, R.D. (2005) Mediator comes of age. **TiBS 30**:221.

212. Kornberg, R.D. (2005) Mediator and the mechanism of transcriptional activation. **TiBS 30**:235-239.

213. Ackerson, C.J., Sykes, M.T., and Kornberg, R.D. (2005) Defined DNA/nanoparticle conjugates. **Proc. Natl. Acad. Sci. USA 102**:13383-13385. PMCID: PMC1200880

214. Takagi, Y., and Kornberg, R.D. (2006) Mediator as a general transcription factor. **J. Biol. Chem. 281**:80-89.

215. Lorch, Y., Maier-Davis, B., and Kornberg, R.D. (2006) Chromatin remodeling by nucleosome disassembly in vitro. **Proc. Natl. Acad. Sci. USA 103**:3090-3093. PMCID: PMC1413907

216. Ackerson, C.J., Jadzinsky, P.D., Jensen, G.J., and Kornberg, R.D. (2006) Rigid, specific, and discrete gold nanoparticle/antibody conjugates. **J. Amer. Chem. Soc. 128**:2635-2640.

217. Takagi, Y., Calero, G., Komori, H., Brown, J.A., Ehrensberger, A.H., Hudmon, A., Asturias, F., and Kornberg R.D. (2006) Head module control of Mediator interactions. **Mol. Cell 23**:355-364.

218. Wang, D., Bushnell, D.A., Westover, K.D., Kaplan, C.D., and Kornberg, R.D. (2006) Structural basis of transcription: Role of the trigger loop in substrate specificity and catalysis. **Cell 127**:941-954. PMCID: PMC1876690

219. Kornberg, R.D. (2007) The molecular basis of eukaryotic transcription (Nobel Lecture). **Proc. Natl. Acad. Sci. USA 104**:12955-12961, and Angewandte Chemie 46:6956-69-65. PMCID: PMC1941834

220. Jadzinsky, P.D., Calero, G., Ackerson, C.J., Bushnell, D.A., and Kornberg, R.D. (2007) Structure of a thiol monolayer-protected gold nanoparticle at 1.1 Å resolution. **Science 318**:430-433.

221. Kornberg, R.D., and Lorch Y. (2007) Chromatin rules. **Nature Structural & Molecular Biology 14**:986-988.

222. Kornberg, R.D. (2007) An autobiographic conversation with Roger D. Kornberg on his work on transcription regulation. **Cell Death Differ. 14**:1977-1980.

223. Kornberg, R.D. (2007) The molecular basis of eucaryotic transcription. **Cell Death Differ. 14**:1989-1997.

224. Boeger, H., Griesenbeck, J., and Kornberg, R.D. (2008) Nucleosome retention and the stochastic nature of promoter chromatin remodeling for transcription. **Cell 133**:716-726. PMCID: PMC2409070

225. Kaplan, C.D., Larsson, K.M., and Kornberg, R,D. (2008) The RNA polymerase II trigger loop functions in substrate selection and is directly targeted by alpha-amanitin. **Molecular Cell 30**:547-556. PMCID: PMC2475549

226. Kaplan, C.D. and Kornberg, R.D. (2008) A bridge to transcription by RNA polymerase. **J. Biology 7**:39. PMCD: PMC2776398

227. Chaban, Y., Ezeokonkwo, C., Chung, W-H., Zhang, F., Kornberg, R.D., Maier-Davis, B., Lorch, Y., and Asturias, F.J. (2008) Structure of a RSC-nucleosome complex and insights into chromatin remodeling. **Nature Struct. & Mol Biol 15**:1272-1277. PMCID: PMC2659406

228. Spahr, H., Calero, G. Bushnell, D.A., and Kornberg, R.D. (2009) Schizosacharomyces pombe RNA polymerase II at 3.6 Å resolution. **Proc. Natl. Acad. Sci. 206**:9185-9190. PMCID: PMC2684843

229. Selth, L.A., Lorch, Y., Ocampo-Hafalla, M.T., Mitter, R., Shales, M., Krogan, N.J., Kornberg,R.D., and Svejstrup, J.Q. (2009) An Rtt109-independent role for Vps75 in transcription-associated nucleosome dynamics. **Mol. Cell. Biol. 29**:4220-4234. PMCID: PMC2715805

230. Wang, D., Bushnell, D.A., Huang, X., Westover, K.D., Levitt, M., and Kornberg, R.D. (2009) Structural basis of transcription: Backtracked RNA polymerase II at 3.4 Å resolution. **Science 324**:1203-1206. PMCID: PMC2718261

231. Liu, X., Bushnell, D.A., Wang, D., Calero, G., and Kornberg, R.D. (2010) Structure of an RNA polymerase II-TFIIB complex and the transcription initiation mechanism. **Science 327**:206-209 PMCID: PMC2813267

232. Huang, X., Wang, D., Weiss, D.R., Bushnell, D.A., Kornberg, R.D., and Levitt, M. (2010) RNA polymerase II trigger loop residues stabilize and position the incoming nucleotide triphosphate in transcription. **Proc. Natl. Acad. Sci. USA 107**:15745-15750. PMCID: PMC2936645

233. Ackerson, C.J., Jadzinsky, P.D., Sexton, J.Z, and Kornberg, R.D. (2010) Synthesis and biocom-jugation of 2 and 3 nm-diameter gold cluster compounds. **Bioconjugate Chem. 21**:214-218.

234. Lorch, Y., Maier-Davis, B., and Kornberg, R.D. (2010) Mechanism of chromatin remodeling . **Proc. Natl. Acad. Sci. USA 107**:3458-3462. PMCID: PMC2817641

235. Liu, X., Bushnell, D.A., Silva, D.A., Huang, X., and Kornberg, R.D. (2011) Initiation complex structure and promoter proofreading. **Science 333**:633-7.

236. Ehrensberger, A.H. and Kornberg, R.D. (2011) Isolation of an activator-dependent, promoter-specific chromatin remodeling factor. **Proc. Nat. Acad. Sci. USA 108**:10115-20.

237. Imasaki, T., Calero, G., Cai, G., Tsai, K.L., Yamada, K., Cardelli, F., Erdjument-Bromage, H., Tempst, P., Berger, I., Kornberg, G.L., Asturias, F.J., Kornberg, R.D., and Takagi, Y. (2011) Architecture of the Mediator head module. **Nature 475**:240-3.

238. Levi-Kalisman, Y., Jadzinsky, P.D., Kalisman, N., Tsunoyama, H., Tsukuda, T., Bushnell, D.A., and Kornberg, R.D. (2011) Synthesis and characterization of $Au_{102}(p\text{-MBA})_{44}$ nanoparticles. **J. Am. Chem. Soc. 133**:2976-82.

239. Hulkko, E., Lopez-Acevedo, O., Koivisto, J., Levi-Kalisman, Y., Kornberg, R.D., Petterson, M., and Hakkinen, H. (2011) Electronic and vibrational signatures of the $Au_{102}(p\text{-MBA})_{44}$ cluster. **J. Am. Chem. Soc. 133**:3752-5.

240. Lorch, Y., Griesenbeck, J., Boeger, H., Maier-Davis, B., and Kornberg, R.D. (2011) Selective removal of promoter nucleosomes by the RSC chromatin remodeling complex. **Nat. Struct. Mol. Biol. 18**:881-5.

241. Liu, X., Bushnell, D.A., and Kornberg, R.D. (2011) Lock and key to transcription: Sigma – DNA interaction. **Cell 147**:1218-9.

242. Gibbons, B.J., Brignole, E.J., Azubel, M., Murakami, K., Voss, N.R., Bushnell, D.A., Asturias, F.J., and Kornberg, R.D. (2012) Subunit architecture of general transcription factor TFIIH. **Proc. Natl. Acad. Sci. USA 109**:1944-9.

243. Murakami, K., Gibbons, B.J., Davis, R.E., Liu, X., Robinson, P., Kaplan, C.D., and Kornberg, R.D. (2012) Tfb6, a new component of the general transcription factor TFIIH, is a nuclear mRNA export factor. **Proc. Natl. Acad. Sci. USA 109**:4816-21.

244. Larson M.H., Zhou J., Kaplan C.D., Palangat, M., Kornberg, R.D., Landick, R., and Block S.M. (2012) Trigger loop dynamics mediate the balance between the transcriptional fidelity and speed of RNA polymerase II. **Proc. Natl. Acad. Sci. USA 109**:6555-60.

245. Robinson, P.J.J., Bushnell, D.A., Trynka, M.J., Burlingame, A.L., and Kornberg, R.D. (2012) . Structure of the Mediator Head Module Bound to the Carboxy-Terminal Domain of RNA Polymerase II. **Proc. Natl. Acad. Sci. USA 109**:17931-5.

246. Murakami, K., Calero, G., Brown, C.R., Liu, X., Davis. R.E., Boeger, H., and Kornberg, R.D. (2013) Formation and fate of a complete, 31-Protein, RNA polymerase II transcription initiation complex. **J. Biol. Chem. 288**:6325-6332.

247. Murakami, K., Elmlund H, Kalisman, N., Bushnell, D.A., Adams, C.M., Azubel, M., Elmlund, D., Levi-Kalisman, Y., Liu, X., Gibbons, B.J., Levitt, M., and Kornberg, R.D. (2014) Architecture of an RNA polymerase II transcription pre-initiation complex. **Science 342**:709.

248. Azubel, M., Koivisto, J., Malola, S., Bushnell, D.A., Hura, G.L., Koh, A.L., Tsunoyama, H., Tsukuda, T., Pettersson, M., Häkkinen, H., and Kornberg, R.D. (2014) Electron Microscopy at Atomic Resolution. **Science 345**:909-12.

249. Schweikhard, V., Meng, C.A., Murakami, K., Kaplan, C.D., Kornberg, R.D., and Block, S.M. (2014) TFIIF and TFIIS promote transcript elongation by RNA polymerase II via synergistic and independent mechanisms. **Proc. Natl. Acad. Sci. USA 111**:6642-7.

250. Lorch, Y., Maier-Davis, B., and Kornberg, R.D. (2014) Specificity of chromatin remodeling and the formation of nucleosome-free regions. **Genes & Development 28**:2492-7.

251. Murakami, K., Mattei, P-J., Davis, R.E., Jin, H., Kaplan, C.D. and Kornberg, R.D. (2015) Uncoupling promoter opening from start site scanning. **Molecular Cell 59**: 133-138.

252. Lorch, Y. and Kornberg, R.D. (2015) Chromatin-Remodeling and the Initiation of Transcription. **Quarterly Reviews of Biophysics Discovery** 48:465-70. PMID: 26537406

253. Fazal, F.M., Cong, M.A., Murakami, K., Kornberg, R.D. and Block, S.M. (2015) Real-Time Observation of the Initiation of RNA Polymerase II Transcription. **Nature 525**:274-7.

254. Murakami, K., Tsai, K.-L., Kalisman, N., Bushnell, D.A., Asturias, F.J., and Kornberg, R.D.(2015) Structure of an RNA polymerase II pre-initiation complex. **Proc. Natl. Acad. Sci. USA** 112:13543-8. PMID: 26483468

255. Eagen, K.P., Hartl. T.A., and Kornberg, R.D. (2015) Stable chromosome condensation revealed by chromosome conformation capture. **Cell, 163**:934-46. PMID: 26544940

256. Robinson, P.J.J., Trnka, M.J., Pellarin, R., Greenberg, C.H., Bushnell, D.A., Davis, R., Burlingame, A.L., Sali, A., and Kornberg, R.D. (2015) Molecular Architecture of the Yeast Mediator Complex. **eLife** Sep 24;4. pii: e08719. PMID: 26402457

257. Azubel, M. and Kornberg, R.D. (2016) Synthesis of Water-Soluble, Thiolate-Protected Gold Nanoparticles Uniform in Size. **Nano Lett. 16**:3348-51.

258. Robinson, P.J., Trnka, M.J., Bushnell, D.A., Pellarin, R., Davis, R., Mattei, P.-J., Burlingame, A.L., and Kornberg, R.D. (2016) Structure of a Complete Mediator-RNA Polymerase II Pre-Initiation Complex. **Cell 166**:1411-22.

259. Nagai, S., Eagen, K.P., and Kornberg, R.D. (2017) Chromatin Potentiates Transcription. **Proc. Natl. Acad. Sci. USA**, in press.

260. Podoly, E., Eagen, K.P., Chen, D.-H., Qiu, J., and Kornberg, R.D., Biocompatible Gold Nanoparticles and Their Use in Electron Microscopy. Submitted.

261. Eagen, K.P., Aiden, E.L., and Kornberg, R.D. (2017) Polycomb-Mediated Chromatin Loops Revealed by a Sub-Kilobase Resolution Chromatin Interaction Map. Submitted.

Exhibit B

Materials Considered by Roger D. Kornberg, Ph.D.

1. Materials and references cited in my declaration

2. Petition for *Inter Partes* Review of U.S. Patent No. 6,331,415 (Paper No. 2)

3. Expert Declaration of John Fiddes, Ph.D., *Mylan Pharm. Inc. v. Genentech, Inc.*, IPR2016-00710 (Exhibit 2019)

4. Expert Declaration of Reiner Gentz, Ph.D., *Mylan Pharm. Inc. v. Genentech, Inc.*, IPR2016-00710 (Exhibit 2021)

5. Patent Owners' Response (Paper No. 31)

6. U.S. Patent No. 6,331,415 (Exhibit 1001)

7. Institution of Inter Partes Review, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624, Paper 15 (Feb. 5, 2016) (Exhibit 2003)

8. Declaration of Jefferson Foote, Ph.D., in Support of Sanofi And Regeneron's Petition for *Inter Partes* Review of U.S. Patent No. 6,331,415 (Exhibit 1006)

9. Declaration of Kathryn Calame, Ph.D., in Support of Mylan Pharmaceuticals Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 6,331,415 (Exhibit 1059)

10. Maniatis, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory (1982) (Exhibit 1095)

11. Southern and Berg, *Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under Control of the SV40 Early Region Promoter*, Journal of Molecular and Applied Genetics, 1:327-341 (1982) (Exhibit 1004)

12. Deposition of John Fiddes Ph.D., taken in IPR2016-00710 (Exhibit 1113)

13. U.S. Patent No. 4,237,224 (Ex. 1005)

14. Wigler et al., *Transfer of purified herpes virus thymidine kinase gene to cultured mouse cells*, Cell 11(1):223-32 (1977) (Exhibit 1096)

15. Wigler et al., *Transformation of mammalian cells with genes from procaryotes and eucaryotes*, Cell 16(4):777-85 (1979) (Exhibit 1097)

16. U.S. Patent No. 4,399,216 (Ex. 1018)

17. Riggs and Itakura, *Synthetic DNA and Medicine*, American Journal of Human Genetics, 31:531-538 (1979) (Exhibit 1003)

18. U.S. Patent No. 4,495,280 (Exhibit 1002)

19. Walter L. Miller. *Use of Recombinant DNA Technology for the Production of Polypeptides*, Adv. Exp. Med. Biol., 118: 153-174 (1979) (Exhibit 1098)

20. Rice and Baltimore, *Regulated Expression of an Immunoglobulin K Gene Introduced into a Mouse Lymphoid Cell Line*, Proceedings of the National Academy of Sciences USA, 79:7862-7865 (1982) (Exhibit 1020)

21. Oi et al., *Immunoglobulin Gene Expression in Transformed Lymphoid Cells*, Proceedings of the National Academy of Sciences USA, 80:825-829 (1983) (Exhibit 1031)

22. Ochi et al., *Transfer of a Cloned Immunoglobulin Light-Chain Gene to Mutant Hybridoma Cells Restores Specific Antibody Production*, Nature, 302:340-342 (1983) (Exhibit 1021)

23. Pauza et al., *Genes Encoding Escherichia Coli Aspartate Transcarbamoylase: The pyrB-pyrI Operon*, Proceedings of the National Academy of Sciences USA, 79:4020-4024 (1982) (Exhibit 1072)

24. Wild et al., *A Mutation in the Catalytic Cistron of Aspartate Carbamoyltransferase Affecting Catalysis, Regulatory Response and Holoenzyme Assembly*, Nature, 292:373-375 (1981) (Exhibit 1073)

25. Roof et al., *The Organization and Regulation of the pyrBI Operon in E. Coli Includes a Rho-Independent Attenuator Sequence*, Molecular and General Genetics, 187:391-400 (1982) (Exhibit 1075)

26. Turnbough et al., *Attenuation Control of pyrBI Operon Expression in Escherichia coli K-12*, Proc. Natl. Acad. Sci. USA, 80:368-372 (January 1983) (Exhibit 1099)

27. Navre and Schachman, *Synthesis of Aspartate Transcarbamoylase in Escherichia Coli: Transcriptional Regulation of the pyrB-pyrI Operon*, Proceedings of the National Academy of Sciences USA, 80:1207-1211 (1983) (Exhibit 1076)

28. Deposition of John Fiddes, Ph.D. taken in IPR2015-01624 (Exhibit 1116)

29. Institution Decision (Paper No. 13)

30. Deposition of Reiner Gentz taken in IPR2015-01624 (Exhibit 1115)

31. Expert Report of John Fiddes, Ph.D., in *Bristol-Myers Squibb Company v. Genentech, Inc., and City of Hope*, Case No. 2:13-cv-05400-MRP-JEM (Exhibit 1144)

32. Shi-Hsiang Shen, *Multiple Joined Genes Prevent Product Degradation in Escherichia coli*, Proc. Nat'l Acad. Sci. (USA) 81:4627-4631 (1984) (Exhibit 2070)

33. Deposition of Reiner Gentz, taken in IPR2016-00710 (Exhibit 1114)

34. Brigitte von Wilcken-Bergmann et al., *A Synthetic Operon Containing 14 Bovine Pancreatic Trypsin Inhibitor Genes Is Expressed in E. coli*, EMBO J. 5(12):3219-3225 (1986) (Exhibit 2071)

35. EP 1 532 260 B1 (Exhibit 2005)

36. Baptist, et al., *Identification of the Salmonella typhimurium cysB Gene Product by Two-Dimensional Protein Electrophoresis*, J. Bacter. 151:495-499 (July 1982) (Exhibit 1100)

37. Mosher, et al., *Synthesis and Secretion of Thrombospondin by Cultured Human Endothelial Cells*, J. Cell Biol. 93:343-348 (May 1982) (Exhibit 1101)

38. Kornberg, *Chromatin Structure: Oligomers of the Histones*, Science 184:865 (1974) (Exhibit 1102)

39. Kornberg, *Chromatin Structure: A Repeating Unit of Histones and DNA*, Science 184:868 (1974) (Exhibit 1103)

40. Thomas & Kornberg, *An octamer of histones in chromatin and free in solution*, Proc. Nat'l Acad. Sci. USA 72:2626 (1975) (Exhibit 1104)

41. Stenesh, *Dictionary of Biochemistry*, 203, 205, 220, 256 (1975) (Exhibit 1071)

42. Henderson's Dictionary of Biological Terms at 274 (9th ed. 1979) (Exhibit 1105)

43. Stenesh, Dictionary of Biochemistry and Molecular Biology at 312, 333 (2nd ed. 1989) (Exhibit 1106)

44. Dorland's Illustrated Medical Dictionary at 1206 (31st ed. 1990) (Exhibit 1107)

45. Tirri, et al., Elsevier's Dictionary of Biology at 443 (1st ed. 1998) (Exhibit 1108)

46. Kahl, G., The Dictionary of Gene Technology Terms at 305 (2001) (Exhibit 1109)

47. King, et al, Dictionary of Genetics at 288 (7th ed. 2006) (Exhibit 1110)

48. Declaration of John Fiddes, Ph.D., submitted in connection with IPR2015-01624 (Exhibit 1145)

49. Exhibit 5 to the deposition of Reiner Gentz, taken in IPR2015-01624 (Exhibit 1141)

50. Exhibit 6 to the deposition of Reiner Gentz, taken in IPR2015-01624 (Exhibit 1142)

51. Exhibit 7 to the deposition of Reiner Gentz, taken in IPR2015-01624 (Exhibit 1143)

52. Frank, B.H., et al., *Two Routes for Producing Human Insulin Utilizing Recombinant DNA Technology*, Munch. Med. Wschr., 125, Suppl. 1:S14-S20 (1983) (Exhibit 2012)

53. Berg, *Dissections and Reconstructions of Genes and Chromosomes*, Science, 213:296-303 (1981) (Exhibit 1069)

54. Mulligan, R.C., & Berg, P., *Expression of a Bacterial Gene in Mammalian Cells*, Science 209: 1422-1427 (1980) (Exhibit 1120)

55. '715 (Morrison) File History, 1/3/92 Response and Oi & Morrison Declarations (Exhibit 1111)

56. '715 (Morrison) File History, 8/23/93 Response and Herzenberg Declarations (Exhibit 1112)

57. '715 (Morrison) File History, 11/1/94 Office Action (Exhibit 1147)