United States District Court,
W.D. Wisconsin.

PROMEGA CORPORATION,
Plaintiff.
v.
NOVAGEN, INC,
Defendant.

No. 96-C-0164-C

Feb. 28, 1997.

Patentee brought action for infringement of two patents for biotechnological inventions relating to protein synthesis. Parties moved for summary judgment. The District Court, Crabb, J., held that: (1) patents were infringed; (2) fact questions precluded summary judgment on issue of whether patentee engaged in inequitable conduct; (3) fact questions precluded summary judgment on issue of anticipation of patents; and (3) fact questions precluded summary judgment on issue of obviousness of patents.

Defendant's motion for summary judgment denied; plaintiff's motion for summary judgment granted in part and denied in part.

Infringed.

Michael E. Hussman, J. Donald Best, J. Christopher Carraway, Michael, Best & Friedrich, L.L.P., Milwaukee, WI, for Plaintiff.

James R. Cole, Nicholas J. Seay, Anthony A. Tomaselli, Sarah E. Coyne, Quarles & Brady, Madison WI, for Defendant.

OPINION AND ORDER

CRABB**, District Judge.**

This is a civil action for injunctive and monetary relief in which plaintiff Promega Corporation alleges that defendant Novagen, Inc. infringed its patents for biotechnological inventions relating to protein synthesis. The parties have filed cross-motions for summary judgment on the validity, enforceability and infringement of the two patents held by plaintiff, United States Patents Nos. 5,324,637 ('637) and 5,492,817 ('817). The action arises under the patent laws of the United States. 35 U.S.C. s.s. 1-371. Jurisdiction is present. 28 U.S.C. s.s. 1331 and 1338(a).

In its motion for summary judgment, defendant contends that plaintiff's patents are invalid because: plaintiff

engaged in inequitable conduct by affirmatively misrepresenting experimental facts to the United States Patent and Trademark Office; plaintiff's claims are anticipated by the prior art; and plaintiff's claims are obvious to those skilled in the art. Alternatively, defendant asserts that if plaintiff's patents are not covered by the prior art, defendant's products do not infringe plaintiff's patents. Plaintiff contests all these arguments vigorously in a series of its own motions for summary judgment. For the reasons articulated below, I conclude that: 1) the term "coupled transcription and translation" as used in plaintiff's patent claims covers reactions in which "any" simultaneous transcription and translation occurs; 2) plaintiff did not intend to limit the scope of its patent claims to the exact sequential order set forth therein; 3) defendant's STP2 and Amersham system products infringe plaintiff's patents; 4) plaintiff did not engage in inequitable conduct by submitting the First Declaration of Dr. Gregory Beckler to the patent office or by failing to submit the Perara and Lingappa reference; 5) there is a material dispute of fact precluding summary judgment with respect to whether plaintiff engaged in inequitable conduct by submitting the Second Declaration of Dr. Gregory Beckler to the patent office; 6) the Lewis et al. reference does not anticipate plaintiff's patent claims; 7) there is material dispute of fact precluding summary judgment with respect to whether the Stueber et al., Coen et al. and Perara and Lingappa references anticipate plaintiff's patent claims; 8) there is a material dispute of fact with respect to whether the Baranov et al. patent application by itself or in combination with the Suzuki reference renders plaintiff's patent claims obvious; and 9) the Baranov et al. patent application cannot be combined with the Lewis et al. reference to render plaintiff's patent claims obvious. A trial will be necessary to resolve the outstanding issues of anticipation, obviousness and inequitable conduct. Anticipation and obviousness will be tried to a jury; the court will try the issue of inequitable conduct.

To succeed on a motion for summary judgment, the moving party must show that there is no genuine issue of material fact and that the moving party is entitled to judgment as a matter of law. Fed.R.Civ.P. 56(c); Celotex Corp. v. Catrett, 477 U.S. 317, 322, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986); Indiana Grocery, Inc. v. Super Valu Stores, Inc., 864 F.2d 1409, 1412 (7th Cir.1989). The non-movant must do more than present some evidence on an issue it asserts is disputed. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 249-50, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986) ("[T]here is no issue for trial unless there is sufficient evidence favoring the non-moving party for a jury to return a verdict for that party. If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted."). A primary purpose of the summary judgment rule is to "isolate and dispose of factually unsupported claims or defenses," Celotex, 477 U.S. at 323-24, 106 S.Ct. 2548, a purpose as salutary in patent cases as in any other area of litigation. Chore-Time Equipment, Inc. v. Cumberland Corp., 713 F.2d 774, 778-79 (Fed.Cir.1983); *see also* Conroy v. Reebok Int'l Ltd., 14 F.3d 1570, 1575 (Fed.Cir.1994).

UNDISPUTED FACTS

A. *Parties*

Plaintiff Promega Corporation and defendant Novagen, Inc. are Wisconsin corporations with their principal places of business in Madison, Wisconsin. Plaintiff is in the business of manufacturing and selling products to biological researchers. Defendant is in the business of manufacturing and selling products for use in gene expression.

B. *Background*

In all known living organisms, genetic information is carried in one or more long molecules of a chemical named DNA. These long molecules of DNA are known as chromosomes. Each chromosome comprises a

number of subunits called genes. Each gene contains information that can be used to synthesize a single, specific protein. Genes help to synthesize new proteins by a process known as expression, which is composed of two parts, transcription and translation.

Proteins are the fundamental "action" molecules of living cells. Proteins are used both for structural purposes within cells and as enzymes that make the other chemical constituents of cells. The basic organization of all proteins is the same. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called amino acids, that are linked together covalently. The chemical bonds linking amino acids together are called peptide bonds. A polypeptide is two or more amino acids linked by a peptide bond. The identity of a protein and its chemical characteristics are determined by the exact sequence in which amino acids are linked in a polypeptide chain. Although there are only 20 amino adds, they are strung together in different orders to produce the hundreds of thousands of proteins found in nature. Although both polypeptides and proteins are composed of amino acid chains, proteins can be distinguished because they contain the complete sequence of amino acids making up that protein and have sometimes undergone post-translational modifications.

Transcription and translation is the essential method for protein synthesis in all cellular life forms. Transcription begins when messenger RNA polymerase (mRNA) binds to a DNA segment known as a promoter and makes a copy of that information. Translation is the transformation of that mRNA transcript into a protein. Messenger RNA is translated into proteins by large structures called ribosomes that bind to the mRNA. The ribosomes and associated molecules read the information in the mRNA, shifting along the strand of mRNA and adding the specified amino acids to a growing polypeptide.

Living organisms can be divided broadly into two large groups, prokaryotes and eukaryotes. Prokaryotes are unicellular organisms that lack a nucleus, such as bacteria. Eukaryotes have a nucleus and include higher life forms such as plants and animals. The nucleus of a eukaryotic cell contains a membrane separating the DNA in the nucleus from the rest of the cellular components.

A major difference between prokaryotes and eukaryotes is the method by which they process DNA into proteins. In prokaryotic cells, the ribosomes and associated molecules that make proteins from mRNA can come into contact with the DNA. This permits translation and transcription to be "coupled," in the sense that as an mRNA strand is being transcribed from DNA, the protein assembly machinery can begin to work simultaneously on the same mRNA strand, translating the mRNA into protein. In eukaryotic cells, the DNA is confined within the nucleus, while the protein assembly machinery of the cell is located outside the nucleus, in the cell's cytoplasm. In eukaryotic cells, the mRNA is transcribed in the nucleus and then is transported by cellular mechanisms into the cytoplasm outside the nucleus for translation. Thus, in eukaryotic organisms, the transcription and translation processes take place at physically separate regions within the cell.

With the advent of modern biotechnology, scientists became interested in reproducing proteins not only inside living organisms but in test tubes also, referred to as "in vitro" experimentation. Various researchers performed transcription and translation in vitro reactions and developed the tools and techniques for such reactions.

Numerous patents and patent applications in the field of biotechnology involve specific proteins or methods for making and using proteins. Many valuable proteins occur in nature only in minute quantities, or are difficult to purify from natural sources. Therefore, a goal of many biotechnology inventions is to devise

methods to synthesize useful quantities of specific proteins by controlling the mechanism by which living cells make proteins.

C. *United States* Patent 5,324,637

On June 28, 1994, the United States Patent and Trademark Office granted plaintiff UnitedStates Patent 5,324,637. The '637 patent includes 76 claims that measure and define the protection afforded by the patent. Claims I through 67 are method claims defining specific methods for coupling transcription and translation. Claims 68 through 76 are product claims defining specific products used in methods for coupling transcription and translation. The relevant claims of the '637 patent read as follows:

1. A method for coupling transcription and translation in a cell-free extract derived from cells from the group consisting of plant and animal cells in a static reaction to produce protein, said method comprising

adding a DNA template to said extract,

adding ribonucleotide triphosphates to said extract,

adding a RNA polymerase to said extract, and

adding a sufficient amount of a magnesium salt to said extract to raise the magnesium concentration to a level where RNA is transcribed from said template DNA and the RNA translates into said protein.

2. The method of claim I wherein said extract is rabbit reticulocyte lysate.

3. The method of claim 2 wherein said final magnesium concentration is about 2.5 mM [millimolar] to about 3.5 mM.

4. The method of claim 2 wherein said final magnesium concentration is about 2.6 mM to about 3.0 mM.

5. The method of claim 2 wherein a polyamine is added to said lysate.

6. The method of claim 5 wherein said polyamine is added to spermidine.

7. The method of claim 6 wherein said spermidine is added to said lysate to a concentration of about 0.2 mM to about 0.4 mM.

8. The method of claim 2 wherein the potassium concentration of said lysate is adjusted to about 40 mM to about 100 mM.

11. The method of claim 2 wherein said polymerase is selected from the group consisting of SP6, T7 and T3 RNA polymerases.

16. The method of claim 2 wherein said DNA template is in a form which is selected from the group consisting of a supercoiled molecule, a covalently closed circular molecule, a linear molecule or a DNA segment made by the process known as a polymerase chain reaction.

17. The method of claim 2 wherein 0.4 mM of each of said ribonucleotide triphosphates are added to said lysate.

34. A method for producing protein from a DNA template having a specific polymerase promoter sequence through coupled transcription and translation in a batch reaction, said method comprising the steps of preparing a solution of eukaryotic cell-free extract of cells selected from the group consisting of plant and animal cells, modifying said extract solution with sufficient concentrations of said template DNA having a specific polymerase promoter sequence, ribonucleotide triphosphates, amino acids and a polymerase corresponding to said promoter sequence of said template DNA, and adding a sufficient amount of a magnesium salt to said extract solution to raise the final magnesium concentration to a level where RNA is transcribed from said DNA template and said RNA translates into protein.

36. The method of claim 34 wherein said extract is rabbit reticulocyte lysate.

37. The method of claim 36 wherein said final magnesium concentration is about 2.5 mM to about 3.5 mM.

38. The method of claim 36 wherein said final magnesium concentration is about 2.6 mM to about 3.0 mM.

39. The method of claim 36 wherein a polyamine is added to said solution.

40. The method of claim 39 wherein said polyamine is spermidine.

42. The method of claim 36 wherein the potassium concentration of said solution is adjusted to about 40 mM to about 100 mM.

45. The method of claim 36 wherein an RNA polymerase is added to the lysate.

46. The method of claim 45 wherein said polymerase is selected from the group consisting of SP6, T7 and T3 RNA polymerases.

47. The method of claim 36 wherein said DNA template is in a form which is selectedfrom the group consisting of a supercoiled molecule, a covalently closed circular molecule, a linear molecule or a DNA segment made by the process known as a polymerase chain reaction.

48. The method of claim 36 wherein said DNA template has a multiple cloning region.

68. A kit for producing protein from a DNA template through coupled transcription and translation, said kit comprising the following components adapted to be used in a batch reaction: eukaryotic cell-free extract of cells selected from the group consisting of plant and animal cells, ribonucleotide triphosphates, RNA polymerase, and magnesium salt at a concentration whereby RNA is transcribed from DNA and RNA translates into protein.

70. A kit as set forth in claim 69 wherein said magnesium salt has a concentration of about 2.5 mM to about 3.5 mM.

76. A eukaryotic cell-free extract for producing protein from a DNA template through coupled transcription and translation in a batch reaction, said extract comprising: cells selected from the group consisting of plant

and animal cells, ribonucleotide triphosphates, RNA polymerase, and a sufficient amount of a magnesium salt to raise the final magnesium concentration to a level where RNA is transcribed from the DNA template and RNA translates into protein.

The specification of the '637 patent states:

Col. 1, lines 21-25: In prokaryotic cells (bacteria) transcription and translation are "coupled", meaning that RNA is translated into protein during the time that it is being transcribed from the DNA.

Col 2, lines 4-7: Prokaryotic E. coli cell-free systems are considered "coupled" because transcription and translation occur simultaneously after the addition of DNA to the extract.

The specification of the '637 patent teaches that the critical component in successful coupling of transcription and translation in eukaryotic systems is the concentration of magnesium ions in the reaction mixture. Magnesium occurs naturally in most rabbit reticulocyte lysates, typically in the range of 4.2 to 5.0 mM. Production of protein does not occur when magnesium concentrations present in the standard lysate are left unchanged. The inventive concept claimed in the '637 patent is that the control of the magnesium concentration makes the difference between the success and failure of the coupled transcription and translation reaction.

Plaintiff's expert witnesses have testified that the term "coupled transcription and translation" as used in the key, independent claims of plaintiff's patent refers to:

a reaction in which RNA is translated into protein during the same time period in which it is being transcribed from a DNA template in one reaction vessel.

Defendant's expert witnesses have testified to much the same definition. Dr. David H.L. Bishop stated that:

Coupled has been applied to situations where both transcription and translation occur in the same reaction tube and at the same time and under specified conditions.

Dr. Carl W. Anderson remarked that:

Coupled suggests that events are spatially and (most likely) temporally linked so that they do or appear to occur simultaneously in the same reaction vessel.

Dr. Robert Mierendorf explained that:

The term "coupled" transcription/translation refers to a reaction in which RNA is produced from a DNA template and translated into protein in the same vessel over a single incubation period.

D. *United States* Patent 5,492,817

On February 20, 1996, the United States Patent and Trademark Office granted plaintiff United States Patent 5,492,817. The '817 patent includes 17 claims that measure and define the protection afforded by the patent. Claims 1 through 12 are method claims. Claims 13 through 17 are product claims. The relevant claims state:

1. A method for coupling transcription and translation in a eukaryotic cell-free extract to produce protein in a static reaction comprising the steps of:

adding a DNA template to the extract;

adding ribonucleotides triphosphates to the extract;

adding a RNA polymerase to the extract; and

adding a sufficient amount of magnesium salt to the extract to raise the magnesium concentration to a level where RNA is transcribed from the DNA template and RNA translates into protein.

3. The method of claim 1 wherein the RNA polymerase is selected from the group consisting of SP6, T7 and T3 RNA polymerases.

13. A kit for producing protein from a DNA template through coupled transcription and translation, said kit comprising the following components adapted to be used in a batch reaction: eukaryotic cell-free extract, ribonucleotide triphosphates, RNA polymerase, and magnesium at a concentration whereby RNA is transcribed from the DNA template and RNA translates into protein.

The specification of the '637 and '817 patents are identical and the claims are similar. Plaintiff filed the application for the '817 patent to extend its claims in the '637 patent to all eukaryotic cell-free extracts, rather than just the plant and animal cell-free extracts of the '637 patent. The principal difference between the claims of the two patents is that the claims of the '817 patent would cover cell-free extracts from eukaryotes that are not plants or animals, such as yeast.

E. *Prior Art*

Before plaintiff applied for a patent on its protein synthesis product, separate transcription and translation systems were known in the prior art. In separate transcription and translation reactions, DNA is transcribed into RNA in a transcription reaction and the RNA from the transcription mixture is then added to a second reaction, a translation reaction. This type of process would not be considered "coupled" as that term is used in this case, but would be considered a "linked" or "two-step" process. Plaintiff marketed two-step transcription and translation kits for some time before filing the patent application that became the '637 patent.

The "References Cited" section of plaintiff's '637 patent lists one foreign patent document, Russian PCT patent application, WO91/02076 (European Patent No. 0593757A1) (Baranov et al. patent application), as well as a number of "other publications" that include: Zubay, G. (1973) Ann.Rev.Genet., vol. 7, p. 267; Pelham, H.R.B. and Jackson, R.J. (1976) Eur. J. Biochem., vol. 67, p. 247; Walter, P. and Blobel, G. (1983) Meth. Enzymol, 96, 84; Glass, C.A. and Pollard, K.M. (1990) Promega Notes 26; Roberts, B.E. and Paterson, B.M. (1973) Proc.Natl.Acad.Sci. USA, vol. 70, p. 2330; Anderson, C., et al. (1983) Meth. Enzymol, 101,635; Krieg, P. and Melton, D. (1984) Nucl. Acids Res., vol. 12, p. 7057; Roberts, B.E., et al. (1975) Proc.Natl.Acad.Sci. USA, vol. 72, p.1922-1926; Pelham, H.R.B., et al. (1978), Eur. J. Biochem, vol. 82, pp. 199-209; Spirin, et al. (1988) Science, vol. 242, pp. 1162-1164; Ryabova, et al. (1989) Nucl.Acid.Res., vol. 17, No. 11, 4412; Baranov, et al. (1989) Gene, vol. 84, pp. 463-466; Suzuki, J. Biochem., vol. 82, pp. 251-260 (1977). The "Background of the Invention" section of the '637 patent

describes some but not all of the work done by others on in vitro transcription and translation reactions, explaining that in vitro systems were available in the prior art.

1. ***The Lewis et al. reference***

J.B. Lewis, C.W. Anderson, J.F. Atkins and R.F. Gesteland published a paper in 1974 entitled *The Origin and Destiny of Adenovirus Proteins,* Cold Spring Harbor Symp. Quant. Biol. 39, 581-90 (1974). Plaintiff did not include this reference in its application for the '637 patent. The Lewis et al. paper describes a study of the proteins produced by a particular class of virus known as adenoviruses. In studying the proteins produced by adenoviruses, the researchers sought to use DNA from the virus to make proteins, without reproducing the virus itself. The paper includes a section entitled "Coupled Protein Synthesis From SV40 DNA," discussing a linked transcription and translation reaction in a fractionated mammalian cell-free system. Lewis et al. used a DNA template composed of DNA from the SV40 virus and a cell-free extract of mammalian cells made from purified fractions different from the cell-free extracts disclosed in the '637 and '817 patents. Ribonucleotide triphosphates (abbreviated "ATP," "GTP," "CTP" and "UTP"), 60 (micro)g/ml of RNA polymerase and 5.6 mM of magnesium acetate were added to the reaction mixture. The paper reports that with the addition of the template SV40 DNA, a number of "polypeptides" were synthesized and that "incorporation of amino acid into polypeptide was significantly stimulated by SV40 DNA...." The paper does not report that "proteins" were produced. The experiments performed in this section of the paper were not intended to optimize a coupled transcription and translation system, but rather were designed to study the proteins produced by adenoviruses.

2. ***The Roberts et al. reference***

The 1975 Roberts et al. reference teaches those skilled in the art to synthesize proteins or polypeptides coded by SV40 DNA by performing two sequential reactions, i.e., linked transcription and translation reactions. The first step is a transcription reaction lasting 15 minutes under reaction conditions optimize for transcription. The second step is a translation reaction performed by changing the reaction conditions to optimize them for translation, including changing the temperature and magnesium salt concentration and adding a wheat germ extract. The transcription and translation reactions are separated temporally. There is no suggestion in the reference for changing the time or reaction conditions of either the transcription or translation reaction. Nor is there any suggestion what reaction conditions would be used if one wished to combine the two reactions.

3. ***The Pelham and Jackson reference***

The 1976 Pelham and Jackson reference defined the preparation of rabbit reticulocyte lysate. Today, rabbit reticulocyte lysate is the most popular form of cell-free extract from eukaryotic cells used for in vitro protein translation.

4. ***The Roberts and Paterson reference***

The most practical alternative to rabbit reticulocyte lysate is a wheat germ extract, described in the 1973 Roberts and Paterson reference.

5. ***The Krieg and Melton reference***

The 1984 Krieg and Melton reference describes a linked transcription and translation system. A transcription

reaction is performed first under conditions optimal for transcription. Then, mRNA is purified from the products of that transcription reaction. Next, the purified mRNA is added to the translation reaction, with conditions optimized for translation. In Krieg and Melton, there is no opportunity for transcription to occur during translation.

6. ***The Coen et al. reference***

Coen et al., Proc.Natl.Acad.Sci. USA, vol. 74, 5487-5491 (1977) teaches those skilled in the art to synthesize proteins coded by DNA fragments by performing linked transcription and translation reactions. The Coen et al. reference is not cited in either the '637 or '817 patents. The first step in the Coen procedure is a transcription reaction for 30 minutes under conditions optimized for transcription, after which conditions are changed to optimize them for translation, including changing the temperature and magnesium salt concentration, and the translation reaction is performed. There is no suggestion in the reference concerning what conditions to use if the two reactions were combined. The reference does not present any data demonstrating that transcription occurs after the initial 15-minute step. The reference teaches that the purification step in Krieg and Melton is unnecessary.

Defendant conducted seven experiments related to the Coen reference. None of the experiments replicated the exact conditions reported in the Coen piece. Defendant used different components. The first experiment consisted of several reactions using various DNA templates. The second experiment consisted of several reactions during which RNA synthesis was monitored at various times. The experiment showed that if the label 3H-CTP is added at the beginning of the transcription reaction, there appears to be a slight amount of degradation of RNA during the translation reaction and incorporation takes place. The third experiment involved several reactions using different DNA templates at different concentrations. Defendant performed two sequential reactions of the type described by Coen as well as modified reactions in which the two Coen reactions were combined. Protein synthesis was measured by incorporation data and gel analysis. Only two of the five templates produced any specific protein. The fourth experiment consisted of several reactions using dual DNA templates. Defendant performed two sequential reactions of the type described by Coen and also performed modified reactions in which the two Coen reactions were combined. Protein synthesis was determined by gel analysis. The fifth experiment was the same as the third except that this time defendant used 5 (micro)g plasmid and measured incorporated counts as well as a gel analysis.

7. ***The Stueber et al. reference***

D. Stueber, et al., Embo J., 3:3143-3148 (1984) is a 1984 piece that teaches those skilled in the art to utilize a protein expression system by performing linked transcription and translation reactions. The Stueber reference is not cited in either the '637 or '817 patents. The first step is a transcription reaction for 20 minutes at conditions optimized for transcription. Then the conditions are altered by changing the temperature and magnesium salt concentration and the translation reaction is performed. The paper does not provide any suggestions on how to change the reaction conditions in order to perform the reactions at the same time. The paper does not contain any explicit suggestion that transcription occurs after the initial 20-minute first step. The reference shows that the purification step in Krieg and Melton is unnecessary.

8. ***The Perara and Lingappa reference***

Eve Perara and Vishwanath R. Lingappa, *A Former Amino Terminal Signal Sequence Engineered to an Internal Location Directs Translocation of Both Flanking Protein Domains,* J. Cell. Biol., 101, 2292-2301 (1985) discloses a linked transcription and translation system involving two separate reactions. The Perara

and Lingappa reference describes the authors' recreation of the Krieg and Melton experiments. The two references differ in that Perara and Lingappa leave out the final purification step before performing the second and separate translation step. Plaintiff never submitted the Perara and Lingappa reference to the patent examiner. There is no recognition in the article that either of the reactions is coupled.

Defendant conducted four experiments related to this reference. (None of the experiments replicated the exact conditions reported in the Perara and Lingappa piece. Defendant used different components and different concentrations of a number of components.) The first experiment consisted of several reactions in which defendant varied the magnesium concentration of the translation reaction. The second experiment consisted of several reactions in which defendant varied the time allowed for the transcription reaction. In the third and fourth experiments, defendant compared the experiments of Perara and Lingappa to standard and modified STP2 (defendant's gene expression product) reactions.

The Perara and Lingappa reference did not come to plaintiff's attention until defendant's counsel pointed it out to plaintiff in a letter dated March 6, 1995. At that time, the '637 patent had issued but the '817 patent was still being prosecuted in the Patent & Trademark Office. Dr. Gregory Beckler, one of plaintiff's scientists, reviewed the Perara and Lingappa reference, concluding that it presented no new information relevant to the claims of plaintiff's proposed patent and that it was cumulative and less material than Krieg & Melton. Plaintiff informed defendant of this conclusion a letter dated April 25, 1995. Plaintiff's kit claims in the '817 patent each require a polymerase, template and extract, just as Perara and Lingappa's experiment does.

9. ***The Baranov et al. patent application***

Another piece of prior art is a published Russian PCT patent application, WO91/02076 (European Patent No. 0593757A1), referred to here as the Baranov et al. patent application. The Baranov et al. patent application describes a coupled transcription and translation system that is intended to operate in a continuous flow mode. In a continuous flow mode reaction, the protein assembly machinery, or cell-free extract, is placed inside a porous membrane with DNA and other constituents necessary for transcription and translation. Then a buffer is permitted to flow through the membrane to wash out the protein produced and to introduce into the reaction additional raw materials for manufacture of additional protein. In this type of system, some components of the system are continuously added and some are continuously removed as protein is translated over extended periods of time. In contrast, a batch reaction (the type of reaction in the '637 and '817 patents) is carried out under one set of conditions in a contained volume. Batch reactions can be run in a small reaction volume, usually twenty-five to fifty microliters, and are often completed in one to two hours.

In the Baranov et al. patent application continuous flow system, the lysate components necessary for sustained protein synthesis are retained by a semipermeable membrane of an ultrafiltration unit. Example 4 of the Baranov et al. patent application includes two sets of materials, an "incubation mixture" and "buffer A." The incubation mixture is combined in an ultrafiltration unit with buffer A, which contains ingredients necessary for the coupled reaction. Buffer A is pumped continuously through the ultrafiltration unit, into the incubation mixture and out through the semipermeable membrane. The continuous flow of Buffer A lasts 34 hours. Protein synthesis does not begin immediately but continues throughout the 34 hours once it has started. The membrane is permeable to CAT specific protein, which has a molecular weight of about 30,000 Daltons. Magnesium ions have a molecular weight of 58 Daltons. Thus, the membrane is permeable to magnesium also. The dialysis of buffer A through the Baranov continuous flow system proceeds at rate of

1.5-2.0 mls an hour. The initial volume of reaction mixture in the reaction chamber is 0.5. ml.

The second ingredient in buffer A is magnesium acetate (MgAc2), which Baranov et al. report is included in buffer A at a concentration of 1.5 mM. The concentration of magnesium for the initial reaction conditions of Baranov et al. is determined by the concentration of magnesium contained in the rabbit reticulocyte lysate of the incubation mixture plus the magnesium contained in buffer A. The concentration of magnesium in any given rabbit reticulocyte lysate may vary; standard rabbit reticulocyte lysate has a magnesium concentration of 4.2 to 5.0 mM. Baranov et al. does not provide the concentration of magnesium in the rabbit reticulocyte lysate used. Dr. Lyuba Ryabova, a co-inventor on the Baranov et al. patent application who performed the experiment described in example 4, has verified that 1.5 mM of magnesium was added to Buffer A in example 4. Ryabova arrived at the conclusion that 1.5 mM was the proper amount of magnesium to add to Buffer A by performing a series of batch reactions using varying amounts of magnesium. The Baranov et al. patent application does not discuss or suggest how one would convert its continuous flow system to a batch reaction and it does not disclose either the magnesium concentration of its initial reaction conditions or the concentration of magnesium that should be used for a batch reaction.

10. ***The Baranov et al. Gene reference***

Baranov et al. (1989) Gene, vol. 84, pp. 463-466 describes experiments involving naturally coupled, prokaryotic cell extract and *E. coli* RNA polymerase.

11. ***The Suzuki reference***

The Suzuki, J. Biochem., vol. 82, pp. 251-260 (1977) reference teaches that the magnesium concentration of rabbit reticulocyte lysates used for translation should be optimized for optimum translational efficiency and fidelity. The reference teaches also that the magnesium concentration should be optimized for each individual lysate since results can vary from one lysate to another.

F. *Plaintiff's and Defendant's Products*

While plaintiff's application for the '637 patent was pending, plaintiff was selling the commercial embodiment of the application as its "TNT" kit. Defendant subsequently offered its own one-step coupled transcription and translation product under the name "STT" (Single Tube Protein). Upon learning that its '637 patent had been approved, plaintiff wrote to defendant, advised it of the forthcoming issuance of the patent and asserted that defendant's STP system was an infringement of the '637 patent. On the basis of that representation, defendant withdrew its product from the market.

In late 1994, defendant introduced a new product, now referred to as "STP2." Defendant tried to design STP2 to avoid infringement of the '637 patent. Defendant has another product similar to the STP2, called the Amersham system, which defendant manufactures and sells to a company named Amersham. The protocols for each product are substantially the same. Both state that the product is designed for in vitro synthesis of proteins from DNA templates containing a bacteriophage T7 or SP6 RNA polymerase promoter and can be used to express proteins from supercoiled plasmids, covalently closed plasmids or products of PCR. Both the STP2 and the Amersham systems use a two-step reaction. First, the user of the kit combines a transcription mix including ribonucleotide triphosphates, RNA polymerase and magnesium salt with a DNA template and performs a transcription reaction for 15 minutes. In this step, no simultaneous transcription and translation occurs. Following the completion of the transcription reaction, the user adds a sample of the reaction products from the transcription reaction, in unpurified form, to a translation mix (consisting of

rabbit reticulocyte lysate, amino acids, and nucleotides). This translation step continues for 60 minutes. The translation reaction is a static or batch reaction. During the translation reaction, there is sometimes simultaneous transcription and translation, but not always. When the ingredients are combined in the second step, the magnesium concentration is 2.74 mM.

By letter dated February 16, 1995, plaintiff informed defendant that the STP2 system infringed the '637 patent just as the STP system had. Defendant responded in a letter dated March 6, 1995, denying plaintiff's accusations. Plaintiff sent another letter to defendant dated April 25, 1995, reasserting its infringement claims. Defendant responded the same way in a letter dated June 19, 1995. No further communication took place until plaintiff filed this suit in February 1996.

G. *Patent Application History*

Plaintiff filed its original patent application (S.N.775, 136) on October 11, 1991. On March 10, 1992, the examiner of the United States Patent and Trademark Office rejected nearly all of the claims of plaintiff's original patent application, explaining that the invention as claimed in the patent application was anticipated by Baranov et al. (the patent application) and obvious over the work of Baranov et al., in view of Suzuki. The examiner asserted that the Baranov et al. patent application method would result in protein production even without the continuous flow dialysis described therein. Plaintiff responded that Baranov did not include any information useful for setting up a batch reaction. The examiner rejected plaintiff's application a second time on November 3, 1992, stating:

Applicants [sic] remarks do not clearly indicate that Baranov et al. protocol described in the prior art does not work. A Declaration stating the results of the use of the Baranov et al. patent showing the Examiner that the protocol in the prior art cannot work as suggested in the rejection [i.e., as a batch mode] should be submitted if this is what Applicant means.

On February 3, 1993, plaintiff appealed the examiner's decision to the United States Patent Office Board of Appeals and Interferences. Plaintiff filed a reply brief on April 14, 1993, explaining that "coupling means the simultaneous transcription of RNA from a template DNA and the translation of that RNA into a protein." In that same reply brief, plaintiff refers interchangeably to the Baranov et al. "reference," "method" and "patent." On February 23, 1994, in a change of strategy, plaintiff withdrew the appeal and filed a continuation application to bring the patent application back to the examiner. The continuation application was assigned a new serial number (S.N.149, 715). Legally and conceptually, the patent application remained the same but the examiner examined it anew. Plaintiff amended its claims to limit them to batch reactions and supplemented its earlier record and arguments with respect to all the rejections entered by the examiner, including those based in whole or in part upon the Baranov et al. patent application. Plaintiff submitted a series of declarations, including one by Dr. Josephine Grosch explaining that plaintiff's product was a commercial success and two by Dr. Gregory Beckler describing his attempts to convert the continuous flow transcription translation reaction of Baranov et al. to a batch reaction.

Dr. Grosch declares in part:

More than 75 scientific experts in a variety of disciplines and R & D Magazine editors selected the commercialized invention TNT Coupled Reticulocyte Lysate System as one of the 100 most technically significant new products of the year.

The commercialized invention TNT Coupled Reticulocyte Lysate System had total sales of over $600,000 in the product's first year and over $1,000,000 in its second year.

Beckler's first declaration (The First Declaration of Dr. Gregory S. Beckler), signed by him on February 22, 1994, contains the following statements:

I am familiar with the Baranov et al. reference ("Baranov") and its disclosed subject matter in that Promega conducted research for over a year, which included the work of myself and other scientists, in attempting to duplicate the results of Baranov in order to develop and commercialize *in vitro* continuous translation/transcription kits based on prokaryotic and eukaryotic extracts. The majority of these experiments at Promega were done using the naturally coupled, transcription/translation prokaryotic *E. Coli* S30 extract ...

Promega then abandoned its efforts on getting the Baranov process to work and switched its research focus to eukaryotic extracts. After approximately five months of research using eukaryotic extracts, the key to coupling transcription and translation in a static reaction, Mg concentration, was discovered. Optimization of the claimed method took approximately another four months.

Prior to the development of the claimed method at Promega, I became convinced that the Baranov method would not work as a continuous transcription/translation system with the information provided as did other researchers in the translation field. During the period from 1991-1992, I discussed the Baranov method, i.e. continuous-flow cell-free (CFCF) with other researchers in the translation field. Many researchers had tried the Baranov procedure without any success. Researchers I spoke with questioned the validity of the method, which became evident in a 1992 publication ... On the first page of the [1992] publication, the authors reference the CFCF coupled transcription/translation system of Spirin and his co-workers. This [sic] the same work as in the Baranov reference. Baranov is a co-worker of Spirin and this technology is most often known in the translation field as the Spirin work because Spirin is the head of the Russian scientists working on CFCF ...

Promega scientists never attempted to run the Baranov system with a eukaryotic extract in a static mode. During the development of the claimed method at Promega and at the time the parent application to the above-identified patent application was filed, I did not believe the Baranov system could be converted to a static system and actually work to produce protein due to Promega and other researchers [sic] problems in getting the system to work in a continuous mode;

Further, it is my opinion that the conditions disclosed in the Baranov reference would not work for eukaryotic extracts under static conditions ...

Part of Beckler's first declaration refers to RNA polymerase and magnesium concentrations that are the concentrations found in example 4 of the Baranov et al. patent application.

In his second declaration (The Second Declaration of Dr. Gregory S. Beckler), dated March 10, 1994, Beckler states in part:

I designed and performed two experiments in an attempt to convert the continuous transcription/translation reaction of the Baranov reference to a batch reaction.

The first experiment (hereafter "Reaction 1") utilized the incubation mixture alone as defined in Baranov Example 4. The second experiment (hereafter "Reaction 2") utilized the incubation mixture and buffer A as defined in Baranov Example 4. See Exhibit 1 attached hereto for Table A which shows the components, concentrations, and amount added for a 0.5 ml batch Baranov incubation mixture. See Exhibit 2 attached hereto for Table B which shows the components, concentrations, and amount added for a 0.5 ml batch Baranov buffer A.

The text of the declaration does not mention that exogenous magnesium was not added to buffer A in Reactions 1 and 2, although that information is contained in table B attached to the declaration. (Tables A and B are appended to this opinion). The second line of table B shows that the only magnesium used in the reactions was the 1.53 mM of magnesium inherently present in the rabbit reticulocyte lysate. Beckler had read the '637 patent application before submitting his declarations. That application stated, "Leaving magnesium concentrations at levels present in the standard lysate, protein production does not occur."

In Reaction 1, Beckler utilized the incubation mixture alone as defined in Baranov example 4 but changed some of the concentrations of the ingredients in attempts to make the mixture work in batch mode. For this first experiment, Beckler added the incubation mixture to water instead of buffer A. (The constituents of the incubation mixture as prepared by Baranov et al. and by Beckler are set forth in attached table A. The ingredients of buffer A as prepared by Baranov et al. and by Beckler are set forth in attached table B.) In Reaction 2, Beckler used the incubation mixture and buffer A as defined in Baranov example 4 (again changing the ingredient concentrations to account for the conversion to batch mode), plus water to make 0.5 ml (13.15(micro)l). Beckler did not add any exogenous magnesium acetate to buffer A but relied instead on the magnesium concentration present in the reticulocyte lysate. Beckler used a 60 % volume of a special Promega reticulocyte lysate (Flexi(R)) that has a magnesium concentration of 2.5 mM to achieve a final magnesium concentration of 1.53 mM. Beckler completed a gel autodiagram showing that no protein was produced using the conditions of Baranov.

On March 11, 1994, plaintiff's attorneys Dave Smith and Billy Jean Strandt and plaintiff's employees Greg Beckler and John Schulz met with United States Patent and Trademark Office examiner Robert Wax and supervisory examiner David Schmichel. Plaintiff submitted the Second Declaration of Dr. Gregory Beckler in person at that time. The Examiner's Interview Summary Record reports that the second Beckler declaration demonstrates that "Baranov et al. as a static reaction does not work." Relying on that information, the examiner decided that he had erred in rejecting plaintiff's claims and withdrew that rejection. On March 22, 1994, the patent examiner issued a "Statement of Reasons for Allowance" stating:

Applicants have submitted declaration by Beckler that indicates that the Baranov et al. method of *in vitro* protein synthesis does not work as described. By performing the reaction as directed in the Baranov et al. reference, but in a batch mode, applicants have demonstrated that no protein is produced. Applicants had also presented evidence that the Baranov et al reference could not be used with some experimentation to produce proteins as is described in the reference in the continuous mode. As the reference did not enable those of ordinary skill in the art to make protein either in batch as claimed nor much protein in a continuous mode as detailed in the prior art the instant invention is not obvious over that reference. Applicants have presented additional data that indicates the invention is a commercial success.

On June 28, 1995, plaintiff's attorneys filed the same Beckler declaration asking the patent examiner to allow its '817 patent. On September 26, 1995, the patent office issued a "Notice of Allowability," citing the same reasons for allowing the patent as mentioned with respect to the '637 patent.

Dr. Robert C. Mierendorf, one of defendant's scientists, reviewed Dr. Beckler's reports of his attempt to replicate the experiments of Example 4 of the Baranov et al. patent application and convert it to batch mode. Under Mierendorf's direction, scientists for defendant replicated Beckler's "Reaction 2" experiment as Mierendorf understood it. These same scientists performed the same experiment with the addition of exogenous magnesium in the amount of 1.5 mM in the Buffer A as specified by Baranov et al. These experiments showed that if Beckler had added exogenous magnesium to the reaction mixture, protein would have been produced. Mierendorf reviewed the additional experiments performed by Robin Hurst at the plaintiff company on the same issue. Plaintiff's data revealed that its experiments yielded the same result as defendant's experiments, i.e., protein is produced when 1.5 mM of exogenous magnesium is added to Buffer A.

In deposition testimony, Beckler acknowledged that he had never attempted to duplicate the Baranov et al. patent method in a continuous flow mode. Two of plaintiff's scientists, doctors John Van Herwynen and Tom Van Oosbree, attended a talk in June 1990 by Dr. Alexander Spirin (a colleague of Baranov). Van Herwynen and Van Oosbree submitted a two-page written report to Beckler that explained, among other things, that "eukaryotic systems can be supplemented with SP6 or T7 RNA polymerases and perform better than prokaryotic systems."

OPINION

I. INFRINGEMENT

[1] [2] Each party has moved for summary judgment on plaintiff's claim that defendant's STP2 and Amersham system products infringe plaintiff's '637 and '817 patents. As the patent owner, plaintiff has the burden of proving infringement by a preponderance of the evidence. ZMI Corp. v. Cardiac Resuscitator Corp., 844 F.2d 1576, 1582 (Fed.Cir.1988). The determination whether a patent claim has been infringed involves two steps: 1) the scope and meaning of the claim are construed without regard to the accused product; and 2) the claim is compared with the accused product to determine whether all of the limitations of the claim are present either exactly or by substantial equivalents. Carroll Touch, Inc. v. Electro Mechanical Sys., Inc., 15 F.3d 1573, 1576 (Fed.Cir.1993); Lemelson v. General Mills, Inc., 968 F.2d 1202, 1206 (Fed.Cir.1992). The first inquiry is a legal question; the second is factual. Markman v. Westview Instruments, Inc., 517 U.S. 370, 116 S.Ct. 1384, 1393, 134 L.Ed.2d 577 (1996) (citations omitted).

A. *Claim Construction*

[3] [4] [5] [6] [7] [8] Construction of the claims precedes all subsidiary questions, including validity and infringement. In re Hayes Microcomputer Products, Inc. Patent Litigation, 982 F.2d 1527, 1541 (Fed.Cir.1992). Claim construction allows a court to elaborate on a patentee's "normally terse language" in the patent claims in order to understand and explain, but not to change, the scope of those claims. Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1580 (Fed.Cir.1991). In construing the scope and meaning of patent claims, a court should consider three sources: the claims, the specification and the prosecution history. Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed.Cir.1995), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996) (citations omitted). The key terms of a claim are to be interpreted according to their ordinary and accustomed meaning to those skilled in the art, unless it appears from the specification that the inventor used them differently. Beachcombers v. WildeWood Creative Prods., Inc., 31 F.3d 1154, 1158 (Fed.Cir.1994); Carroll Touch, 15 F.3d at 1577. Expert testimony may be used to explain how those skilled in the art would interpret the claims. Markman, 52 F.3d at 979 (citation omitted).

A patentee may act as his own lexicographer and define key terms in the patent. As long as the patentee clearly spells out the special definition of a term in the specification and uses the term in the same way in the claims, that definition will be controlling for purposes of claim interpretation. *Id*. at 979.

The parties ask the court to construe two elements of plaintiff's patents. First, the parties seek an interpretation of the term "coupled transcription and translation," a term used in each of the key, independent claims in plaintiff's '637 and '817 patents. (Claim I of both the '637 and '817 patents employs the term "coupling transcription and translation." The distinction between coupled and coupling is immaterial and I will treat the two words as one and the same for purposes of this opinion.) Second, the parties look to the court to decide whether claims 1-6, 8, 11, 16, 34, 36-40, 42 and 45-48 of the '637 patent and claims 1 and 3 of the '817 patent cover only the exact sequential order of the process steps set forth therein.

1. ***Construction of the term "coupled transcription and translation"***

[9] Plaintiff contends that "coupled transcription and translation" means that "DNA is transcribed to RNA and that RNA is translated to protein during the same reaction, i.e. simultaneously." Defendant agrees that "coupled" signifies simultaneous transcription and translation, but suggests that the court must specify whether "coupled transcription and translation" covers reactions in which there is *any* simultaneous transcription and translation or pertains only to reactions in which *all* of the transcription and translation occur simultaneously. According to defendant, if the term encompasses reactions in which "any" simultaneous transcription and translation occurs, plaintiff's patents are covered by the prior art two-step reactions; if the term means that "all" simultaneous transcription and translation must take place in the same reaction, defendant's products do not infringe.

Plaintiff's patents provide little guidance to the precise meaning of the term coupled transcription and translation. The patent claims do not define the term. The specifications of both the '637 and '817 patents signify only that coupled transcription and translation refers to reactions that take place "during the [same] time," or "simultaneously." The prosecution history renders much the same vague insight: plaintiff's reply brief on its appeal of the patent examiner's final rejection of its patent application explains that " 'coupling' means the simultaneous transcription of RNA from a template DNA and the translation of that RNA into a protein." It is apparent that plaintiff intended the term coupled to signify simultaneous transcription and translation. But plaintiff did not spell out clearly in the patent specifications whether coupled transcription and translation should apply to reactions with "any" simultaneous transcription and translation or only to processes in which "all" transcription and translation for the entire experiment take place at the same time. Plaintiff's failure to do so means that it did not act as its own lexicographer on that question and that the term must be accorded its ordinary and accustomed meaning to those skilled in the art.

The definitions of the term "coupled" offered by plaintiff's and defendant's experts do not resolve the dispute. Instead, they tend to suggest that plaintiff's choice of the word "simultaneous" as a synonym for coupled is accurate. Defendant protests that defining coupled transcription and translation merely as simultaneous transcription and translation does not adequately distinguish the reactions in plaintiff's patents from the linked or two-step reactions available in the prior art. According to defendant, claims should be construed to maintain their validity if possible, *see* Whittaker Corp. by Technibilt Div. v. UNR Industries, Inc., 911 F.2d 709, 711 (Fed.Cir.1990), and if the court does not construe the term "coupled" to mean that *all* transcription and translation takes place simultaneously, plaintiff's claims are invalid because they are anticipated by several two-step reaction references, Roberts et al., Perara and Lingappa, Stueber et al. and

Coen et al. I will address defendant's arguments about the invalidity of plaintiff's patents in another section of this opinion and say here only that those arguments do not lead me to construe plaintiff's claims simply to avoid a defense of anticipation. *See* Corning Glass Works v. Sumitomo Elec. U.S.A., 868 F.2d 1251, 1256 (Fed.Cir.1989) (court should not redraft claim to avoid defense of anticipation).

There is nothing in plaintiff's patents indicating that plaintiff intended to limit its use of the term "coupled transcription and translation" to reactions in which all transcription and translation takes place together, i.e., reactions that were not preceded by a separate translation step. If any coupling takes place as a result of the processes that plaintiff describes in its patent claims, then plaintiff's patent claims cover that reaction. As defendant points out, this may pose plaintiff some problems in dealing with the defense of anticipation. But anticipation is not a reason to limit the breadth of plaintiff's claims when the claims themselves appear broad. Thus, to the extent it is necessary to elaborate on the scope of plaintiff's use of the term "coupled transcription and translation," I find the term covers reactions in which there is *any* simultaneous transcription and translation.

2. ***Order of process steps in plaintiff's claims***

[10] The parties dispute whether claims 1-6, 8, 11, 16, 34, 36-40, 42 and 45-48 of the '637 patent and claims 1 and 3 of the '817 patent cover only the exact sequential order of the process steps set forth therein. Defendant asserts that plaintiff's claims must be read to encompass only reactions that follow the specific order laid out in the patent claims. Plaintiff says that defendant's position is too narrow a reading of plaintiff's claims.

In support of its position, defendant cites Loral Fairchild Corp. v. Victor Co. of Japan, Ltd., 906 F.Supp. 798 (E.D.N.Y.1995) and Thorn EMI N. Am., Inc. v. Intel Corp., 928 F.Supp. 449 (D.Del.1996). According to defendant, *Loral* and *Thorn* stand for the proposition that process claims should be limited to the chronological sequence of the steps that make up the claims. In *Loral,* the court explained:

Predominant language norms suggest recounting process steps in a chronological sequence. A process description flows most naturally from one step in the sequence to the next in chronological order. The process step described third in sequence thus generally precedes the step described fourth.

Id. at 805. The court cited this language with approval in Thorn, 928 F.Supp. at 457. However, neither of the courts adopted a position as broad as defendant suggests. Although in *Loral* the court relied on "predominant language norms" to a certain extent, it found other evidence in the patent itself that the patentee intended to specify an exact procedural sequence. Loral, 906 F.Supp. at 805. For example, the court determined that because the "edges of [the] implanted barrier regions" could not be "aligned" with the "vertical edges of the insulation layer" (as required by the patent claim at issue) until the insulation layer was in place, the claim was limited to a process in which the insulation layer always preceded the implanted barrier regions. *Id*. Moreover, language in the specification and in the prosecution history of the patent supported a chronological sequence interpretation of the claim. *Id*. (specification discussed "next" step; prosecution history included dependent claim that mentioned "prior" step). The patent claims at issue in Thorn, 928 F.Supp. 449, were even plainer in specifying an exact sequential order. The steps of the claims were separately ordered (step (a), step (b), etc.) and two of the claims stated step (a) "then" step (b). *Id*. at 457.

There is scant indication in plaintiff's claims themselves that plaintiff intended the patent to cover only the

exact sequential addition of ingredients. If plaintiff had sought to limit its claims to a specific sequence, it could have added language such as "then" or "and thereafter" to the steps of the claim. *See* Bio-Rad Laboratories, Inc. v. Nicolet Instrument Corp., 739 F.2d 604, 614 (Fed.Cir.1984). Without such an indication in the language of the claims themselves, I cannot find that plaintiff intended to limit the scope of its claims in the manner defendant suggests. *See* Vaupel Textilmaschinen KG v. Meccanica Euro Italia S.P.A., 944 F.2d 870, 880 (Fed.Cir.1991) (exact order of steps "not specifically set forth" in claim).

B. *Infringement*

There are two forms of patent infringement: literal infringement and infringement under the doctrine of equivalents. In both cases, the patent owner bears the burden of proving infringement by a preponderance of the evidence. ZMI Corp., 844 F.2d at 1582; 35 U.S.C. s. 271(a). Only literal infringement is at issue in this case.

[11] [12] [13] [14] [15] Patent infringement requires that every element of the patent claim be found in the accused device either literally or equivalently. Johnston v. IVAC Corp., 885 F.2d 1574, 1577 (Fed.Cir.1989); ZMI, 844 F.2d at 1582. Literal infringement requires that the accused device embody every element of a claim. Jurgens v. McKasy, 927 F.2d 1552, 1560 (Fed.Cir.1991) (where all claim limitations are present in the accused device exactly, the claims "read on" the accused device and literal infringement is made out); Johnston v. IVAC Corp., 885 F.2d 1574, 1577 (Fed.Cir.1989) (where a device does not "read on" an accused device exactly there can be no literal infringement). In determining infringement, defendant's product must be compared with the properly construed claims of the patent, not with the patent holder's commercial product or the preferred embodiments described in the specification of plaintiff's patent. Amstar Corp. v. Envirotech Corp., 730 F.2d 1476, 1481-82 (Fed.Cir.1984). The mere addition of elements or functions to an otherwise infringing combination does not negate infringement. *Id*. at 1482. Section 217(b) of Title 35 U.S.C. provides in relevant part that "whoever actively induces infringement of a patent shall be liable as an infringer." Product instructions that direct the user how to use the product in an infringing manner constitute inducement of infringement. Herbert F. Schwarz, *Patent Law & Practice* 78 (1995).

[16] In its initial summary judgment brief, defendant acknowledged that during the second reaction of the STP2 and Amersham system products, some simultaneous transcription and translation takes place. Defendant admitted that if the team "coupled" as used in plaintiff's patents cover reactions in which *any* simultaneous transcription and translation takes place, its products infringe. I have determined that the term "coupled" does cover that type of reaction. Therefore, it would appear that defendant's products infringe. But defendant has backed away from its earlier concession, contending now that its products do not infringe because its products' protocols do not call for the performance of steps in the same order as in plaintiff's claims. Defendant points out that its products do not call for the addition of cell-free extract until the second step of the process, whereas plaintiff's patent claims require that the cell-free extract is the first component of the batch reaction. Similarly, defendant argues that its products call for the addition of magnesium in the first step before any translation takes place whereas plaintiff's claims require magnesium to be the final addition to the reaction mix.

Defendant's argument is foreclosed by the determination as a matter of claim construction that plaintiff's claims are not limited to the specific sequential order in which the process steps are set forth. Defendant's products contain every ingredient named in claims 68, 69 and 70 of the '637 patent and in claim 13 of the '817 patent. Similarly, the protocol of defendant's STP2 and Amersham system products instructs the user to perform each of the steps identified in 1-6, 8, 11, 16, 34, 36-40, 42 and 45-48 of the '637 patent and claims I

and 3 of the '817 patent. It is insufficient that defendant's protocols divide the reactions into two steps: a non-infringing transcription reaction and an infringing translation reaction. The addition of steps to a process that otherwise infringes does not avoid infringement. Accordingly, I find that 1) sale of defendant's STP2 and Amersham system products directly infringes claims 68, 69 and 70 of the '637 patent and claim 13 of the '817 patent and 2) the protocol of defendant's products induce infringement of claims 1-6, 8, 11, 16, 34, 36-40, 42 and 45-48 of the '637 patent and claims 1 and 3 of the '817 patent.

II. PATENT ENFORCEABILITY

[e]ach individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office.....

The failure to cite prior art that is material and known to the applicant can invalidate a patent if the applicant's failure to disclose was motivated by an intent to mislead the Patent and Trademark Office. FMC Corp. v. Manitowoc Co., 835 F.2d 1411, 1415 (Fed.Cir.1987). Inequitable conduct must be both material and intended. Molins PLC v. Textron, Inc., 48 F.3d 1172, 1179 (Fed.Cir.1995). In order to defeat plaintiff's motion for summary judgment, defendant must establish that there is a genuine dispute of fact with respect to both materiality and intent. Braun, Inc. v. Dynamics Corp. of Am., 975 F.2d 815, 822 (Fed.Cir.1992). Proof that an applicant engaged in inequitable conduct must be established by clear and convincing evidence. Id. 975 F.2d at ----, 24 U.S.P.Q.2d at 1127.

[20] [21] [22] [23] [24] [25] Prior art is material where there exists a substantial likelihood that a reasonable examiner would consider the art important in deciding whether to allow the patent application to issue. 37 C.F.R. s. 1.56; Halliburton Co. v. Schlumberger Technology Corp., 925 F.2d 1435, 1440 (Fed.Cir.1991). Materiality does not presume intent; intent must be proven on its own. Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 552 (Fed.Cir.1990). Intent need not be proven by direct evidence; it is most often proven by a showing of acts, the natural consequences of which are presumably intended by the actor. Molins PLC, 48 F.3d at 1180. Intent may be inferred from the facts and circumstances surrounding the applicant's conduct. *Id*. at 1180-81 (citing Paragon Podiatry Laboratory, Inc. v. KLM Laboratories, Inc., 984 F.2d 1182, 1189-90 (Fed.Cir.1993)). The drawing of inferences relies heavily on the fact-finder's assessment of a witness's credibility and character. *Id*. at 1181 (citation omitted). Gross negligence in and of itself does not justify an inference of intent to deceive: "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Kingsdown Medical Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed.Cir.1988); *see also* Hebert v. Lisle Corp., 99 F.3d 1109, 1116 (Fed.Cir.1996) (there must be factual basis for finding of deceptive intent). In making the overall determination whether inequitable conduct has occurred, a court must balance materiality and intent: the more material the omission, the less culpable the intent required. Halliburton Co., 925 F.2d at 1439. When a court determines that inequitable conduct occurred in relation to one or more claims during prosecution of the patent application, the entire patent is rendered unenforceable. Kingsdown Medical Consultants, 863 F.2d at 877.

On March 10, 1992, plaintiff's application for what would become the '637 patent was rejected nearly in full by the examiner of the United States Patent and Trademark Office. Plaintiff did not have much better luck on its second attempt. On November 3, 1992, the examiner rejected plaintiff's application again, explaining that plaintiff had not shown that the Baranov et al. patent application protocol did not work. However, the examiner left plaintiff a window of opportunity, instructing plaintiff to submit a declaration showing that the

Baranov et al. patent application continuous flow method could not work in a batch mode if that is what plaintiff believed. Plaintiff took the hint and submitted a series of declarations from Dr. Gregory S. Beckler explaining that he and other scientists at plaintiff company had conducted a number of experiments using the Baranov method and indeed, Baranov did not work. Plaintiff's declarations achieved their intended goals. On March 22, 1994, the patent examiner issued a "Statement of Reasons for Allowance," announcing that it would grant plaintiff's patent application. The examiner's decision was premised, at least in part, on Beckler's indication that the Baranov patent method did not produce any protein when it was converted to a batch mode. The examiner accepted Beckler's explanation that the Baranov continuous flow method simply did not work in a batch mode.

Defendant finds this turn of events suspicious and argues, in short, the following. Plaintiff's declarations contain outright lies or at least ambiguous and misleading statements. Plaintiff submitted these mistruths because it knew it was the only ticket to patent approval. By submitting these baselesslies to the patent office, plaintiff engaged in inequitable conduct. Without these declarations, the patent office would never have granted plaintiff its patents. In addition to its arguments concerning Beckler's first and second declarations, defendant contends that plaintiff's failure to submit the Perara and Lingappa reference to the patent examiners with respect to its '817 patent application constitutes inequitable conduct. I will take up that argument after discussing the Beckler declarations.

A. *Second Declaration of Dr. Gregory S. Beckler*

[26] Defendant suggests that Beckler's second declaration contains two false statements: 1) that Beckler used the incubation mix of the Baranov et al. patent application experiments and 2) that Beckler used the Buffer A of those same Baranov experiments. According to defendant, Beckler did not use either the incubation mix or the Buffer A of the Baranov et al. patent application method because Beckler omitted the exogenous magnesium that Baranov et al. had added. Plaintiff acknowledges that Beckler's incubation mix did not include exogenous magnesium but employed water instead. Plaintiff admits also that Beckler added no exogenous magnesium to the Buffer A. But there is a rub. Plaintiff explains that Beckler did not add exogenous magnesium because he was attempting to "convert" the Baranov method to a batch mode, rather than attempting to replicate the Baranov experiments exactly. Thus, says plaintiff, Beckler was not lying or misleading anyone when he included these statements in his second declaration.

Defendant fires back that even if Beckler's statements about the use of the Baranov incubation mix and Buffer A were not strictly untrue, they were at least misleading and ambiguous. Defendant points out that Beckler never mentions in his second declaration that he omitted the exogenous magnesium when attempting to convert Baranov to a batch mode. The only place where it can be discerned that plaintiff did not add the exogenous magnesium is a table of ingredients attached to Beckler's second declaration (Table B, appended to opinion). Even there it is not stated explicitly that Beckler did not add exogenous magnesium. Instead, the second line of the table shows that the only magnesium added is the 1.53 mM found naturally in the reticulocyte lysate. According to defendant, plaintiff's failure to address this critical fact explicitly in the text was a "sly and subtle" attempt to bury information in hopes of deceiving the patent examiner. Plaintiff finds it unfortunate that defendant was unable to figure out what was going on with Beckler's experiments, but notes that even defendant's expert Dr. Robert Mierendorf admits that he understood what plaintiff was doing after studying the tables with some degree of care.

As discussed above, in order to prove inequitable conduct, defendant must show by clear and convincing evidence that plaintiff intended to deceive the patent office and that plaintiff's deception had a material

effect on the disposition of its patent application. There is a sliding scale at work: the higher the materiality, the less deceptive intent that defendant needs to show. Materiality is straightforward in this case. Plaintiff's application failed twice before plaintiff submitted Beckler's second declaration showing that the Baranov patent application method did not work in a batch mode. Once that application arrived and the patent examiner accepted what was stated therein, plaintiff's previous failure turned abruptly into a triumphant success. Without a declaration stating that Baranov did not work in the batch mode, plaintiff's chances of receiving a patent were slim to none. Thus, Beckler's second declaration appears highly material to plaintiff's receipt of the '637 patent. (And to the '817 patent for that matter, which would have been rejected also if the patent examiner believed that Baranov worked in the batch mode.)

Intent is the more critical issue here. At this stage of the proceedings, defendant has to provide enough evidence of plaintiff's deceptive intent to show that a genuine dispute of material fact exists for resolution at trial. Although I have serious doubts about defendant's ability to prove plaintiff's deceptive intent by clear and convincing evidence, I am satisfied that defendant has met its burden on summary judgment.

Beckler states explicitly in his second declaration that he was attempting to "convert" Baranov to a batch reaction. In the next paragraph, he explains that he "utilized the incubation mixture and buffer A as defined in Baranov Example 4." However, that was not technically the case, given that Beckler did not add the exogenous magnesium called for in Baranov Example 4. Beckler's initial assertion that he was "convert[ing]" Baranov modifies his later statements about the use of the Baranov incubation mixture and buffer A to some extent. It is difficult to infer a deceptive intent from Beckler's statements that he used Baranov et al. patent application components when in fact he used close approximations of the Baranov components in attempts to convert Baranov to a batch mode, but this does not answer defendant's charge that plaintiff made a deliberate decision to hide the non-inclusion of exogenous magnesium from the patent examiner. Beckler may not have included this information in the text of his second declaration because he believed that it was sufficient to reference the tables that contained the key to understanding that no exogenous magnesium was added. Perhaps he was thinking that the patent examiners were sharp scientists and could figure this out with careful examination (just like Dr. Mierendorf did later). Maybe none of this crossed his mind.

If the exogenous magnesium were simply one of a number of ingredients in the reaction mix, it would be virtually impossible to infer any deceptive intent from Beckler's second declaration. But the exogenous magnesium is not just another ingredient. It is the key ingredient, the ingredient that determines whether the reaction works or not. Part of plaintiff's alleged inventive concept in the '637 and '817 patents is that the addition of exogenous magnesium makes the Baranov et al. continuous flow method work in the batch mode.

Beckler has testified that he believed initially that exogenous magnesium was unnecessary and even counterproductive to the conversion of the Baranov et al. patent application method to a batch mode. As I understand it, Beckler thought that because components are continually added and removed from a continuous flow reaction, Baranov et al. needed to add extra magnesium to keep the magnesium concentration constant. But Beckler believed that in a batch reaction carried out under one set of conditions in a contained volume, there would be enough magnesium in the rabbit reticulocyte lysate to achieve an optimal magnesium concentration and that magnesium concentration would remain constant without the addition of any exogenous magnesium. Although this may be a proposition fully supportable by scientific principles, it strikes a lay person as odd, especially considering that the parties discovered later that when exogenous magnesium is added, the Baranov continuous flow method works fine in a batch mode. Why

Beckler did not try to convert the Baranov patent application method in more than one way is perplexing. When Beckler discovered that the Baranov patent application method would not convert without the exogenous magnesium, he could have attempted the conversion with the exogenous magnesium. If he had done that, he could not have represented to the patent office that the Baranov patent method did not work in a batch mode and plaintiff would not likely have its patents today.

Perhaps the suggestion of what Beckler could have done encroaches upon the forbidden zone of hindsight, but it does not stretch the bounds of reason to draw the inference that Beckler did not do experiments with exogenous magnesium because he knew that if he did, the conversion might work and all would be lost for plaintiff. This might explain also why the non-addition of magnesium is somewhat cryptically encoded in the supporting tables of his declaration rather than in the text. None of this is direct evidence of a deceptive intent, but intent may be inferred from the facts and circumstances of an applicant's conduct and there is a plausible inference of deceptive intent here. Whether to actually draw that inference depends on the assessment of Beckler's credibility, something which will have to await resolution at trial. I remind defendant again that although it has raised a plausible suggestionof deceptive intent, it still must prove plaintiff's deceptive intent by clear and convincing evidence.

Plaintiff attempts to dismiss defendant's suggested implication of deceptiveness by arguing that any potential ambiguities in Beckler's second declaration were resolved at a meeting with the patent examiners on March 11, 1994. According to plaintiff, at that meeting the patent examiners asked multiple questions about Beckler's second declaration and Beckler explained to them explicitly that his experiments did not include the use of any exogenous magnesium. The patent examiners allegedly agreed with Beckler that his conversion techniques were proper. Not surprisingly, defendant argues that plaintiff should not be able to introduce this testimony. Defendant proffers three reasons in support of this argument: 1) the testimony is hearsay, 2) the testimony is not in writing; and 3) allowing such testimony into evidence subverts sound principles of public policy.

[27] Beckler's statement concerning what he told the patent examiners is not hearsay. Plaintiff is offering that testimony to show that the statement was made, not to prove that exogenous magnesium was not added to his experiments. The statement is not being offered to prove the truth of the matter asserted but rather to discount inferences of deceptive intent by showing the absence thereof. However, Beckler's statement concerning what the patent examiners understood is hearsay. Plaintiff attempts to offer that statement to prove that the patent examiners understood that Beckler's experiments lacked exogenous magnesium. The officer's understanding is a matter about which the officers should be testifying.

[28] Defendant cites 37 C.F.R. s.s. 1.2, 1.133, and s. 713.04 of the *Manual of Patent Examining Procedure,* (4th ed. rev.1982) in support of its argument that because all business conducted with the patent office must be in writing, plaintiff cannot introduce testimony concerning any oral communications it may have had with the office. None of these provisions controls the question whether plaintiff may introduce testimony on what Beckler told the examiners about his use of exogenous magnesium. The regulations concern proceedings in front of the patent office, not this court. Although Beckler could have recorded his explanation to the patent examiners in writing, it would not have added much to the credibility of his testimony now. Plaintiff's citation to Litton Systems, Inc. v. Whirlpool Corp., 728 F.2d 1423 (Fed.Cir.1984) is inapposite. In *Litton,* the court barred the patent applicant from introducing testimony about an oral agreement it allegedly reached with the patent office that contradicted the written record directly. Beckler's testimony about his explanation to the patent officers would not contradict evidence in the written patent record. Instead, it would help to elaborate on that written record. Of course, it is necessary to find Beckler's

testimony credible before it has any value, but he will be permitted to offer it.

Defendant's last objection is that because 37 C.F.R. s. 15a.6 prevents it from asking the patent examiners themselves about Beckler's alleged explanation, public policy demands that Beckler's testimony be barred. According to defendant, by allowing Beckler to testify, the court would be setting a precedent that would allow all patentees to prove that they did not engage in inequitable conduct by taking the stand and asserting that they explained away any patent discrepancies during an interview with the patent office.

Defendant is probably correct that 37 C.F.R. s. 15a.6 prevents it from subpoenaing the patent examiners and asking them about what Beckler told them. However, s. 15a.6 says nothing about preventing patent applicants from testifying about what they told the patent examiners. Although defendant's concern that Beckler may simply be making these statements in a self-serving capacity is understandable, Beckler will be under oath while making these statements and he faces perjury charges if he is lying. The credibility of his assertions can be evaluated under the usual standards.

In sum, because Beckler's second declaration is highly material and there is a plausible inference of deceptive intent, I will deny summary judgment to either party and reserve the issue for trial.

B. *First Declaration of Dr. Gregory S. Beckler*

[29] Defendant argues that plaintiff committed inequitable conduct by submitting the First Declaration of Dr. Gregory S. Beckler to the patent office with the intent to deceive or mislead the patent examiners into believing that Beckler had duplicated the Baranov et al. patent application continuous flow method and had determined that the method did not work as described by Baranov in the patent application. Defendant contends that Beckler's first declaration is in direct conflict with his later deposition testimony in which he admits that he never attempted to duplicate Baranov in a continuous flow mode. According to defendant, Beckler's deposition testimony shows that his first declaration was an outright mistruth, with the only explanation for the submission of the declaration being an invidious intent to dupe the patent examiners into thinking that the Baranov patent application was not the crucial piece of prior art that the patent examiners had believed it to be.

Early in his first declaration, Beckler states that he was familiar with the "Baranov et al. reference ('Baranov')" and that he and other scientists at the plaintiff company had spent over a year attempting to "duplicate the results of Baranov" in the continuous flow mode. Unfortunately for the parties and the court, Beckler does not specify which Baranov reference he is referring to in that statement. There are two relevant Baranov prior art references: the Baranov et al. 1989 *Gene* reference and the Baranov et al. Russian PCT patent application. Plaintiff contends that defendant's inequitable conduct argument with respect to Beckler's first declaration cannot get off the ground because defendant is mistaken in its belief that Beckler's reference to "duplicat[ing] the results of Baranov" pertained to the Baranov et al. patent application. Instead, plaintiff explains that any reasonable reader would know that Beckler was referring to Baranov's 1989 *Gene* article at that point of the declaration. If Beckler had in mind the *Gene* reference in that paragraph of the declaration, his deposition testimony is not in conflict because he testified only that he had not attempted to replicate the Baranov continuous flow *patent application* method; it said nothing about attempts to duplicate the continuous flow method described in the Gene reference. Thus, before even arriving at the starting point of the materiality and deceptive intent inquiries it is necessary to decide which Baranov reference is at issue in Beckler's allegedly misleading statement.

There are two important differences between the Baranov et al. *Gene* reference and the Baranov et al. patent application. First, the experiments in the *Gene* reference involve naturally coupled, prokaryotic cell extract while the patent application experiments concern eukaryotic cell extract (wheat germ or rabbit reticulocyte lysate). Second, the *Gene* article experiments involve *E. coli* RNA polymerase while the patent application discusses exogenous phage polymerases, SP6 or T7.

In Beckler's first declaration, the sentence following the allegedly deceptive statement explains that the "majority" of experiments done to duplicate the results of Baranov involved "the naturally coupled, transcription/translation prokaryotic *E. Coli* S30 extract." There are no descriptions of this extract in the Baranov patent application. In contrast, the Baranov *Gene* article states specifically that its experiments involve prokaryotic cell extract. This would seem to be a clear indication that Beckler's statement concerned the Baranov *Gene* reference. "Not so," says defendant. Picking up on the term "majority" of experiments, defendant suggests that plaintiff's choice of language indicates that plaintiff conducted at least some experiments other than the "majority" experiments. Defendant would have the court believe that these other experiments involved other extracts, some of which may have been the eukaryotic type extracts employed in the Baranov et al. patent application experiments and that Beckler was referring to the Baranov et al. patent application. Defendant's fancy linguistic footwork is all show and no substance. Plaintiff's use of the word "majority" does signify that other experiments were conducted. But there is no evidence that these other experiments involved eukaryotic extracts, let alone that these experiments involved the eukaryotic extracts at issue in the Baranov et al. patent application. In fact, Beckler's first declaration contradicts this notion shortly after the allegedly offending statement, when Beckler states that plaintiff "then abandoned its efforts on getting the Baranov process to work and switched its research focus to eukaryotic extracts." If plaintiff had been using eukaryotic extracts in attempting to "duplicate" Baranov, Beckler would not have been making a "switch" to eukaryotic extracts when he abandoned his duplication efforts.

Plaintiff presents another sound reason why Beckler could not have been referring to the Baranov et al. patent application in discussing his "duplication" attempts: timing. In Beckler's first declaration, he states that research was conducted "for over a year" to duplicate the results of Baranov in addition to five months of additional research and four months of optimization work. The Baranov et al. patent application was published only seven months before plaintiff's first application for the '637 patent was filed. Thus, plaintiff asserts, it would have been chronologically impossible for the declaration to be referring to the Baranov et al. patent application. Defendant responds to plaintiff's timing argument with a creative new twist. According to defendant, Beckler knew in June 1990, approximately fifteen months before it filed its patent application in October, 1991, that the Baranov group had begun work with continuous flow coupled systems in eukaryotic extracts. Thus, Beckler could have been conducting Baranov patent type experiments long before the patent application was published. Defendant's argument does not account for the four-month gap between the nearly nineteen months that Beckler claims to have been working on Baranov and the fifteen months that Beckler would have had if he first learned about Spirin and Baranov's new work in June 1990. This gap could be explained if Beckler overstated the amount of time he was working on Baranov but there is no suggestion that he did so. Moreover, it seems unlikely that Beckler would have had all the information he needed to recreate the Baranov patent application experiments in June 1990. Doctors Van Herwynen and Van Oosbree had provided Beckler a report concerning the new information but that report did not list the constituent ingredients included in the later Baranov et al. patent application.

Defendant does have legitimate reasons to believe that Beckler was referring to the Baranov patent application method. The *Gene* article had not been a topic of discussion with the patent office before Beckler's first declaration and it is odd that Beckler would mention it without referring to it specifically.

Beckler uses the same term, "Baranov," later in his first declaration to mean the Baranov patent application and would have clarified this inquiry greatly had he been more specific about the reference to which he was referring. (Beckler's failure to take that five-second step has led to countless hours of extra work for the parties and this court.) Interesting as these points are, they are insufficient to show that Beckler was referring to the patent application.

Even if defendant could show that Beckler's statement referred to the Baranov et al. patent application, defendant lacks the proof required to show materiality and deceptive intent by clear and convincing evidence. In the "Statement of Reasons for Allowance," the patent examiner relied in part on the fact that plaintiff had presented evidence that the Baranov et al. patent method did not produce much protein in a continuous flow mode, but this does not appear to be as crucial as the information that the Baranov et al. patent method could not be converted to a batch mode. In its November 3, 1992 rejection of plaintiff's application, the patent examiner asked plaintiff specifically to present a declaration explaining why the Baranov et al. patent method did not work in batch mode. Plaintiff did so and received its patent, likely as a result of that declaration. The fact that the Baranov et al. patent method did not work as well in the continuous flow approach as Baranov claimed pales in importance to the fact that it did not work at all when converted to batch mode.

Defendant's real problem lies in its duty to show plaintiff was operating under a deceptive or misleading intent. Although I found that the circumstances allowed a plausible inference of deceptive intent to be drawn with respect to Beckler's second declaration, the same cannot be said about the events surrounding the submission of Beckler's first declaration. If anything, Beckler was negligent in failing to specify the Baranov reference to which he was referring. But negligence, even gross negligence, does not amount to deceptive intent in and of itself.

C. *Failure to Cite Perara and Lingappa Reference*

Finally, defendant contends that plaintiff committed inequitable conduct by failing to submit the Perara and Lingappa reference to the patent examiner looking at plaintiff's application for the '817 patent after defendant had made plaintiff aware of that reference. Plaintiff responds that Perara and Lingappa was merely cumulative and essentially the same as the Krieg & Milton reference, the only difference being that the Perara & Lingappa article leaves out the final purification step. As with its argument on Beckler's first declaration, plaintiff lacks sound evidence of materiality and deceptive intent. Even if Perara and Lingappa were the smoking gun reference that defendant makes it out to be, plaintiff's belief that this reference was cumulative (as explained to defendant in a letter dated April 25, 1995) is strong evidence of good faith. There is no circumstantial evidence of deceptive intent in plaintiff's failing to disclose a reference as there was in Molins PLC v. Textron, Inc., 48 F.3d 1172 (Fed.Cir.1995). Plaintiff's mere awareness of Perara and Lingappa does not indicate any deceptive intent in plaintiff's decision not to submit that reference. *See* Halliburton, 925 F.2d at 1443.

III. PATENT VALIDITY

[30] [31] [32] [33] Each claim of a patent carries a presumption of validity. 35 U.S.C. s. 282. The presumption requires "the decisionmaker to employ a decisional approach that starts with acceptance of the patent claims as valid and that looks to the challenger for proof to the contrary." Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1534 (Fed.Cir.1983). A challenger of a patent must establish facts that support a conclusion of invalidity by clear and convincing evidence. Texas Instruments v. United States Int'l Trade Comm'n, 988 F.2d 1165 (Fed.Cir.1993). The challenger's burden is particularly difficult when the prior art

was before the patent examiner during prosecution of the application. Hewlett-Packard Co. v. Bausch & Lomb, Inc., 909 F.2d 1464, 1467 (Fed.Cir.1990). The patentee is entitled to summary judgment on this issue if the challenger fails to present evidence on any material issue relating to validity. Dairyland Power Coop. v. United States, 16 F.3d 1197, 1202 (Fed.Cir.1994).

[34] [35] There are two types of invalidity claims, invalidity for anticipation and invalidity for obviousness. Invalidity for anticipation, 35 U.S.C. s. 102, requires a showing that all of the elements and limitations of the claim can be found within a single prior art reference. In re Paulsen, 30 F.3d 1475, 1478-79 (Fed.Cir.1994); Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed.Cir.1991). Invalidity for obviousness, 35 U.S.C. s. 103, requires a showing that a person of ordinary skill in the art would have known from the prior art references to make the claimed invention; unlike the showing for anticipation, more than one prior art reference may be relevant to the determination. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1137-38 (Fed.Cir.1985); *see also* Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1267 (Fed.Cir.1991) (if more than one reference combined, claim must be tested for obviousness, not anticipation).

A. ***Anticipation***

Under 35 U.S.C. s. 102, a patent is invalid if:

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States....

[36] [37] [38] A claim is anticipated under s. 102 only if each element and limitation of the claim is found within a single prior art reference. Scripps Clinic, 927 F.2d at 1576. A reference anticipates a claim if it discloses the claimed invention sufficiently to allow a skilled artisan to take its teachings in combination with his own knowledge of the particular art and be in possession of the invention. In re Graves, 69 F.3d 1147, 1152 (Fed.Cir.1995), *cert. denied,* 517 U.S. 1124, 116 S.Ct. 1362, 134 L.Ed.2d 528 (1996) (citations omitted). Although extrinsic evidence may be used to show what the reference meant to persons of ordinary skill in the field of the invention, it may not be used to fill gaps in the reference. Scripps Clinic, 927 F.2d 1565, 1576 (Fed.Cir.1991) (citation omitted).

1. ***Testimony of plaintiff's expert witnesses on patent validity***

[39] Before addressing the issue of anticipation, it is necessary to respond to defendant's protestations about the opinions of plaintiff's expert witnesses on patent validity. Defendant argues that the opinions of plaintiff's experts are conclusions based on nothing other than pure speculation. According to defendant, because plaintiff's experts did not conduct any experiments with respect to the crucial pieces of prior art (as did defendant's experts), plaintiff's experts' testimony cannot be relied upon in deciding the outcome of this summary judgment motion.

[40] The first step in deciding whether the opinions of expert witnesses can be used in resolving a summary judgment motion is to decide whether those opinions would be admissible at trial. If the expert has sufficient credentials to offer expert testimony in a given area, the court may rely on proposed facts based on that

expert testimony that are undisputed by the opposing party. However, in certain situations, a court may decide that an expert's opinion is admissible but so devoid of any substance that it does not suffice to raise a genuine issue of material fact for resolution at trial. Khan v. State Oil Co., 93 F.3d 1358, 1365 (7th Cir.1996), *cert. granted in part,* 519 U.S. 1107, 117 S.Ct. 941, 136 L.Ed.2d 831, 1997 WL 63830 (Feb. 18, 1997) ("Weight is different from admissibility. An expert's report might be admissible but so lacking in weight as not to block the granting of summary judgment for the other side."); Mid-State Fertilizer Co. v. Exchange Nat'l Bank of Chicago, 877 F.2d 1333, 1339 (7th Cir.1989) ("an expert's declaration, full of assertion but empty of facts and reasons, won't get a case past a motion for summary judgment, for the judge must look behind [the expert's] ultimate conclusion ... and analyze the adequacy of its foundation."). In those situations, a court may grant summary judgment because it believes that the weight of the expert's opinion is too insignificant to warrant a trial.

That determination is the exception, not the rule. On a summary judgment motion, the court's role is to judge the admissibility of the expert opinion, not to decide conclusively what weight to accord that opinion. The testimony offered by plaintiff's experts is not so inherently lacking in material significance or so patently frivolous that it can be disregarded entirely. The fact that defendant's experts conducted experiments on the prior art may make their testimony more credible than plaintiff's experts who did not recreate the prior art and rely solely on the text of the prior art and their own knowledge, but that is not necessarily so. Plaintiff's experts are not bound to conduct their own experiments before giving expert testimony surrounding the significance of the prior art. Expert opinion based on an examination of the relevant documents is perfectly acceptable.

Defendant raises two distinct anticipation arguments. First, it contends that the Lewis et al. reference, published in 1974, reads on all the key, independent claims of plaintiff's '637 and '817 patents and therefore invalidates those patents by anticipation. Second, it asserts that a series of references discussing linked or two-step transcription and translation reactions anticipate plaintiff's patent claims.

2. *Lewis et al. reference*

[41] The Lewis et al. reference does not teach 1) the use of rabbit reticulocyte lysate or wheat germ as a cell-free extract; 2) a final magnesium concentration of 2.5 mM to 3.5 mM; 3) the use of a polyamine; 4) a final potassium concentration between 40 and 100 mM; 5) the addition of a ribonuclease inhibitor; 6) use of a polymerase selected from the group SP6; T7 and T3 polymerases; or 7) the addition of 0.4 mM of each ribonucleotide triphosphate to the lysate. Accordingly, Lewis does not anticipate claims 2 through 33, 35 through 67 and claims 69-75 of the '637 patent, or claims 3 through 12 and claims 14 through 16 of the '817 patent. However, defendant asserts that the Lewis et al. reference contains each and every step in claims 1, 34, 68 and 76 of the '637 patent and claims 1 and 13 of the '817 patent, thereby anticipating those independent claims.

Plaintiff marshals three basic arguments why the Lewis et al. reference does not anticipate any of these claims. First, plaintiff argues that Lewis leads only to the production of non-specific polypeptide products rather than actual proteins, as required by the patent claims. Second, plaintiff argues that the *Lewis* et al. reference does not include the use of a DNA template with an *E. Coli* promoter as envisioned by the patent claims. Third, plaintiff asserts that Lewis does not teach the use of a cell-free extract as specified by the patent claims.

The Lewis et al. reference reports the syntheses of a number of polypeptides. It does not report the

production of proteins. However, all the key, independent claims at issue in plaintiff's patents require the "produc[tion of] protein." How can this be squared? Defendant's first response is that although there may be a technical distinction between proteins and polypeptides, plaintiff did not have that distinction in mind when employing the word protein in its patent claims; therefore plaintiff meant to include polypeptides within the meaning of protein. Such an argument does not give plaintiff sufficient credit. As defendant is well aware, the choice of language in patent claims requires great care and specificity. It is possible to construe the term "proteins" in plaintiff's patent claims to encompass polypeptides only by assuming that plaintiff did not intend to make a distinction between the two. Plaintiff's lack of specific reference to the distinction in the patents themselves lend some credence to defendant's argument, but plaintiff did not need to clutter its patents with that distinction when it is well-recognized in the art that there exists at least some difference between a polypeptide and a protein. Although both polypeptides and proteins are composed of amino add chains, proteins can be distinguished because they contain the complete sequence of amino acids making up that protein and have sometimes undergone post-translational modifications.

Dr. Carl Anderson, one of the authors of the Lewis et al. reference, has testified that the accurate characterization of what their experiments produced is polypeptides, not protein. This jibes with the language of the Lewis et al. reference itself, which says nothing about the production of proteins. As much as defendant tries to deny it, Anderson's testimony is highly pertinent, especially in conjunction with the language of the Lewis et al. reference. In short, plaintiff's patent claims require the production of protein, not merely polypeptides.

Perhaps anticipating that determination by the court, defendant shifts gears and argues that the reaction described in the Lewis et al. reference did result in the production of protein, albeit a relatively small amount that went unreported in the reference itself. In support of this argument, defendant submits the testimony of Dr. Robert Mierendorf. Mierendorf's theory concerning protein production in the Lewis et al. reference is difficult to grasp. Mierendorf believes that the molecular weight of some of the polypeptides produced in the Lewis reaction is similar to the weight of the large T-antigen proteins found in the Roberts et al. reference, thus signifying that the Lewis products are proteins also. In addition, Mierendorf explains that the size of the small t-antigen protein observed in the Paucha et al. reference corresponds to products observed in the Lewis reaction and that therefore the Lewis polypeptides did include an authentic full length small t-antigen protein.

[42] [43] Whatever the validity of this hypothesis, it remains undisputed that the Lewis et al. reference itself did not report the production of any proteins. This does not mean that defendant's anticipation argument must be discarded. Defendant may still rely on the doctrine of inherent anticipation. Even when a particular limitation of a patent is not disclosed expressly in a prior art reference, "anticipation can occur when [the] claimed limitation is 'inherent' or otherwise implicit in the relevant reference." Standard Havens Prods., Inc. v. Gencor Indus., Inc., 953 F.2d 1360, 1369 (Fed.Cir.1991). The test for inherent anticipation may be stated as follows:

To serve as an anticipation where the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

Continental Can, 948 F.2d at 1268. Although defendant may be correct that the doctrine of inherent anticipation arose from instances of "accidental achievement of a product or process," it is no longer limited

to those situations. *See* Bradford J. Duft & Eric P. Mirabel, *Principles of Inherency*, JPTOS 539 (July 1995). "Inherency may not be established by probabilities or possibilities ... The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Oelrich, 666 F.2d 578, 581 (C.C.P.A.1981).

Mierendorf's testimony is not sufficient to prove that the Lewis et al. reactions "necessarily" produced proteins. His comparison of the molecular weights of the products of the Roberts and Paucha references to the weights of the products of the Lewis reference is complex and involves a number of inferential steps. Although it might be easier for someone skilled in the art to walk that inferential road than for a lay person, defendant has submitted no evidence to suggest that a person of ordinary skill in the art would have concluded that Lewis et al. produced protein. Moreover, defendant has to prove that Lewis necessarily produced protein by clear and convincing evidence. Mierendorf's testimony cannot meet that standard. Accordingly, I find that the Lewis et al. reference does not anticipate plaintiff's patent claims. This determination makes it unnecessary to consider plaintiff's arguments concerning the differences between the DNA template and cell-free extract specified in the '637 and '817 patents and those items in the Lewis et al. reference.

3. *References pertaining to two-step or linked reactions*

[44] In addition to the argument that the Lewis et al. reference anticipates plaintiff's patent claims, defendant contends that four other references anticipate plaintiff's claims as well, Roberts et al., Stueber et al., Coen et al. and Perara and Lingappa. These prior art references resemble one another in that they all involve two-step protein synthesis, a process requiring a transcription reaction or "step" followed by a translation reaction. Plaintiff asserts that although these references involve "linked" transcription and translation, they do not teach "coupled" transcription and translation as defined in plaintiff's patent claims.

I have construed the term "coupled transcription and translation" in plaintiff's patent claims to cover reactions in which "any" simultaneous transcription and translation takes place. Defendant contends that if that is the construction given the term, then if any transcription and translation occurs during the second steps or reactions of these prior art references, the references anticipate plaintiff's claims.

The breadth of the term "coupled transcription and translation" in plaintiff's patent claims raises some problems for plaintiff at this stage. Because I have determined that plaintiff's claims cover reactions in which "any" coupled transcription and translation takes place, plaintiff's claims would be anticipated by any of these prior art references in which "any" coupled transcription and translation occurred. This is subject to one caveat. Because none of these prior art references explicitly mentioned coupled transcription and translation as the term is used in plaintiff's patent claims, defendant must rely again on the doctrine of inherent anticipation. (The Stueber et al. reference is the only one of the four linked reaction references to use the term "coupling" explicitly.But as used in that reference, the term coupling refers to "linked" or "two-step" reactions rather than simultaneous transcription and translation.) This means that in addition to needing to prove by clear and convincing evidence that "any" coupled transcription and translation took place, plaintiff must show also that coupled transcription and translation is a "necessary" result of these prior art reference experiments rather than just a sporadic happenstance. Because defendant appears to have conceded that the Roberts et al. reference did not include any "coupled" transcription and translation, I will give that reference no further consideration. Before analyzing the three other references, the basic science on which defendant relies must be noted briefly. Defendant contends that in each of these three prior art reactions, part of the transcription step is still occurring when the translation step is started. This occurs because the RNA polymerase is not fully inactivated by the time the translation reaction begins, inhibitors

have not accumulated in sufficient quantities to cease transcription and the available ribonucelotide triphosphates have not been exhausted.

a. Stueber et al.

Defendant points out that the first reaction in Stueber is 20 minutes, only five minutes longer than the first reaction in defendant's STP2 and Amersham system products. According to defendant, because it is clear that transcription has not stopped by the second step in its products, it is highly unlikely that transcription would have stopped by the second reaction in Stueber, that five-minute interval is not enough time for transcription to come to a complete halt. Plaintiff rejects this view, citing its expert Dr. Randall Dimond for the proposition that no coupling is taking place in the second step of the Stueber reactions. The parties have proffered reasonable but conflicting expert testimony. The factual dispute is one to be resolved at trial.

b. Coen et al., Perara and Lingappa

Defendant conducted seven experiments to discover whether coupled transcription and translation took place in the second step of the Coen et al. procedures, determining that it did. Plaintiff cries foul, arguing that defendant's experiments were intended to enhance coupling and did not replicate the Coen method faithfully. Defendant responds that plaintiff cannot make such bold assertions when it has not conducted any of its own replications of the Coen reactions. In addition to arguing about coupling, the parties disagree whether the DNA template in Coen had an *E. Coli* promoter, as required by plaintiff's patent claims. The parties' arguments with respect to the Perara and Lingappa reference mirror the arguments concerning Coen et al. The only exception is that plaintiff articulates more explicitly in its Perara and Lingappa arguments that even if some coupling takes place in the second step of these references, defendant has produced no evidence to show that coupling "always" results as required by the doctrine of inherent anticipation.

I cannot say that defendant's replications of the Coen et al. and Perara and Lingappa experiments are so flawed as to be unreliable. They do tend to show that coupling is taking place in the second steps of the experiments. Whether defendant's experiments are reliable replications of the prior art is a question not properly resolved at this stage of the proceedings. A jury must make that determination. The same is true for the parties' DNA template disputes. Expert testimony from each side reasonably supports either position.

B. *Obviousness*

[45] [46] [47] As a prerequisite to validity, 35 U.S.C. s. 103 requires that a patent be non-obvious:

A patent may not be obtained ..., if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

The inquiry required by s. 103 goes to the underlying inventiveness of the proposed patent. Deering, Milliken & Co. v. Temp-Resisto Corp., 274 F.2d 626 (2d Cir.1960). Obviousnessunder 35 U.S.C. s. 103 is a question of law. Para-Ordnance Mfg., Inc. v. SGS Importers Int'l, Inc., 73 F.3d 1085, 1088 (Fed.Cir.1995), *cert. denied,* 519 U.S. 822, 117 S.Ct. 80, 136 L.Ed.2d 38 (1996). However, the analysis of obviousness rests on several factual inquiries: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims at issue; 3) the level of ordinary skill in the art at the time of the invention; and 4) objective evidence of secondary considerations of patentability. *Id., see also* Miles Laboratories, Inc. v. Shandon, Inc., 997 F.2d 870, 877 (Fed.Cir.1993).

1. ***Baranov et al. patent application alone***

[48] Defendant contends that at the time of the invention of the patents-in-suit it would have been obvious to someone of ordinary skill in the art to make the conversion of the Baranov et al. patent application continuous flow method to the batch reaction that plaintiff developed. I have discussed this issue at some length in the section of this opinion concerning defendant's charges of inequitable conduct. Basically, defendant argues that the patent examiner got it right the first time when he denied plaintiff's patent claims as obvious over the Baranov et al. patent application and that he erred when he changed this determination later and granted plaintiff's patents. Plaintiff contends that defendant's argument is based on 20/20 hindsight and that it would not have been obvious to anyone in the art to make the conversion in the manner achieved by plaintiff.

At first, plaintiff attempted to convert the Baranov et al. patent method by leaving out the exogenous magnesium that Baranov et al. teaches is necessary to a continuous flow method. Plaintiff's expert Dr. Beckler has explained why he chose to do this and there may well be scientific merit to his decision. Dr. Beckler failed in his attempts to convert the Baranov et al. patent method without the exogenous magnesium. As a result, plaintiff was able to convince the patent office that Baranov did not render plaintiff's patent claims obvious. However, both plaintiff and defendant realized later that if exogenous magnesium in the amount taught by Baranov is added, the continuous flow method can be converted to a batch method without problems. The question this raises is whether plaintiff or anyone skilled in the art should have recognized that the addition of exogenous magnesium was an obvious way to convert Baranov to a batch mode. Legitimate disputes of fact prevent the resolution of that question on summary judgment.

2. ***Baranov et al. patent application in combination with other references***

[49] [50] When challengers combine prior art references in attempts to show obviousness, they must show " 'some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination.' " Para-Ordnance Mfg., 73 F.3d at 1088 (citation omitted); *see also* Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 934 (Fed.Cir.1990) ("It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor"). "[I]ndividual, naked parts of separate prior art references [cannot be] employed as mosaic to recreate a facsimile of the claimed invention." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1552 (Fed.Cir.1983).

Defendant argues that Baranov in combination with the Lewis or Suzuki references renders plaintiff's claims obvious. Defendant has submitted no evidence to indicate why a person of ordinary skill in the art would have thought to combine Baranov with the Lewis et al. reference. There is nothing in Baranov to suggest its combination with Lewis. Only through the benefit of hindsight does the combination of Baranov and Lewis become as "painfully obvious" as defendant suggests. However, the Baranov et al. patent application does rely heavily on the importance of magnesium concentration, the primary focus of the Suzuki reference. The patent examiner recognized this relationship early in the prosecution history and it remains a close enough link to permit defendant to argue a Baranov/Suzuki combination.

ORDER

IT IS ORDERED that the motion for summary judgment of defendant Novagen, Inc. (Dkt.# 53) is

DENIED. It is further ordered that: 1) the motion for summary judgment of plaintiff Promega Corporation on the validity of its patents (Dkt # 77) is GRANTED with respect to defendant's claim that the Lewis et al. and the Roberts et al. references anticipate plaintiff's patent claims. In addition, the motion is GRANTED with respect to defendant's claim that the Baranov et al. patent application in combination with the Lewis et al. reference renders plaintiff's patent claims obvious. The motion is DENIED with respect to defendant's claim that the Stueber et al., Coen et al. and Perara and Lingappa references anticipate plaintiff's patent claims; 2) the motion for summary judgment of plaintiff Promega Corporation on claim interpretation and infringement (Dkt.# 81) is GRANTED. The term "coupled transcription and translation" as used in plaintiff's patent claims covers reactions in which "any" simultaneous transcription and translation occurs. In addition, plaintiff did not intend to limit the scope of its patent claims to the exact sequential order set forth therein. Accordingly, sale of defendant's STP2 and Amersham system products directly infringe claims 68, 69 and 70 of the '637 patent and claim 13 of the '817 patent. The protocol of defendant's products induce infringement of claims 1-6, 8, 11, 16, 34, 36-40, 42 and 45-48 of the '637 patent and claims 1 and 3 of the '817 patent; 3) the motion for summary judgment of plaintiff Promega Corporation on defendant Novagen, Inc.'s claim of inequitable conduct (Dkt.# 85) is GRANTED with respect to defendant's claim that plaintiff's failure to submit the Perara and Lingappa reference to the patent office constituted inequitable conduct and DENIED with respect to defendant's claim that plaintiff engaged in inequitable conduct by submitting the Second Declaration of Dr. Gregory Beckler to the patent office; 4) the motion for summary judgment of plaintiff Promega Corporation on defendant Novagen, Inc.'s new claim of inequitable conduct (Dkt. # 123) is GRANTED. Plaintiff did not engage in inequitable conduct by submitting the First Declaration of Dr. Gregory Beckler to the patent office; and 5) the motion for summary judgment of plaintiff Promega Corporation on defendant Novagen, Inc.'s new claim of invalidity is DENIED. There is a material dispute of fact with respect to whether the Baranov et al. patent application by itself or in combination with the Suzuki reference renders plaintiff's patent claims obvious.

A jury trial will be held on March 10, 1997, to resolve the remaining issues of anticipation and obviousness and the court will consider the remaining issue of inequitable conduct.

CORRECTED EXHIBIT 1

CORRECTED EXHIBIT 1

TABLE A

Source/Batch#	Component name and #	Final Rx Conc. stated in Barancy	Amount in 0.5ml rx	Volume of Solution Added
Promega, #3374031	Rabbit Reticulocyte Lysate, L455A	60%	------	300ul
Promega	pPOLYACAT plasmid DNA	100ug/ml	50ug	38ul of 1.3mg/ml
Promega, #14920	SP6 RNA Polymerase, P408	30,000u/ml	15,000u	7.5ul of 2,000u/ul
Sigma, #31-19317	Alpha 2 macroglobulin, M-7151	5ug/ml	2.5ug	1.0ul of 2.5mg/ml
Sigma, #19F-0095	Leupeptin, L-2884	5ug/ml	2.5ug	1.0ul of 2.5mg/ml
Sigma, #20H0859	Chymostatin, C-7268	5ug/ml	2.5ug	0.4ul of 6mg/ml
Promega, #328205	RNasin, N2511	50u/ml	25u	0.6ul of 40u/ul
BMB, #13150821-62	Pyruvate kinase, 109 045	0.1mg/ml	50ug	25ul of 2mg/ml

Water was add to make 0.5ml (126.5ul) for Reaction 1.

EXHIBIT 2

EXHIBIT 2

TABLE B

Source/Batch#	Component name and #	Final Rx Conc. as stated in Baranov	Amount in 0.5ml rx	Volume of Solution Added
Sigma #101H-5625	HEPES, pH 7.6, HB091	25mM	------	25ul of 0.5M
Promega, #3374031	MgAc2	1.5mM	-------	1.53mM in retic lysate
Mallinckrodt, #6700 K BCV	KAc2, 6700	100mM	-----	25ul of 2M
Promega, #4177601	ATP, E601B	1mM	-----	5ul of 0.1M
Promega, #136202	GTP, E603B	0.4mM	-----	2ul of 0.1M
Promega, #136302	CTP, E604B	0.4mM	-----	2ul of 0.1M
Promega, #136102	UTP, E602B	0.4mM	-----	2ul of 0.1M
Aldrich, #02208LW	Spermidine, S382-8	0.25mM	-----	1.25ul of 0.1M
Promega, #5511	DTT, V3151	4.0mM	-----	1.1ul of 1M
Promega, #33474031	Creatine phosphate	6.0mM	-----	8.52mM in retic. lysate
Amersham, #3289	[35S]methionine, SJ.1015	20uM	-----	40ul of >1,000Ci/mmol
Promega, #136406	Amino acid mixture minus methionine, L996B	20uM	-----	10ul of 1mM

Water was added to make 0.5ml (13.15ul) for Reaction 2.