PRUETZ LAW GROUP LLP
Adrian M. Pruetz (Bar No. 118215)
ampruetz@pruetzlaw.com
1600 Rosecrans Avenue, 4th Floor
Manhattan Beach, CA 90266
Telephone: (310) 321-7640
Facsimile: (310) 321-7641

QUINN EMANUEL URQUHART OLIVER & HEDGES, LLP
Brian Cannon (Bar No. 193071)
briancannon@quinnemanuel.com
Tun-Jen Chiang (Bar No. 235165)
tjchiang@quinnemanuel.com
555 Twin Dolphin Drive, Suite 560
Redwood Shores, California 94065-2139
Telephone: (650) 801-5000
Facsimile: (650) 801-5100

Attorneys for Defendants and Counterclaimants Roche Molecular Systems, Inc.; Roche Diagnostics Corporation; and Roche Diagnostics Operations, Inc.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

THE BOARD OF THE TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiff,

vs.

ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATION, INC.,

Defendants.

ROCHE MOLECULAR SYSTEMS, INC.; ROCHE DIAGNOSTICS CORPORATION; ROCHE DIAGNOSTICS OPERATION, INC.,

Counterclaimants,

vs.

THE BOARD OF THE TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY; THOMAS MERIGAN AND MARK HOLODNIY,

Counterclaim Defendants.

CASE NO. C-05-04158-MHP

ROCHE'S' RESPONSIVE CLAIM CONSTRUCTION BRIEF

Judge: Hon. Marilyn H. Patel
Date: October 3, 2007
Time
Ctrm: 15, 18th Floor

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Miscellaneous

Defendants and Counterclaimants Roche Molecular Systems, Inc., Roche Diagnostics Corporation and Roche Diagnostics Operations Inc. ("Roche") submit this responsive claim construction brief pursuant to Patent Local Rule 4-5 and the Order re Case Management filed June 5, 2007 (Docket No. 161). In support, Roche submits (1) the Declaration of John G. Bartlett, M.D. (professor of medicine at Johns Hopkins, former Chair of the Division of Infectious Diseases at Johns Hopkins, author of the federal guidelines for HIV therapy and expert in the treatment of HIV/AIDS patients); (2) the Declaration of Jeffrey D. Lifson, M.D. (Head of the Retroviral and Pathogenesis Laboratory at the National Cancer Institute and expert in the application of PCR techniques to HIV research); and (3) the Declaration of Brian C. Cannon, attaching documents.

Preliminary Statement

Each of the three patents claims a polymerase chain reaction ("PCR") assay, the data from which is used by physicians to evaluate the effectiveness of anti-HIV therapy. Specifically, the claims of the patents refer to a method of "evaluating the effectiveness" of anti-HIV therapy for a "patient." The patent claims also include a "conclusion" concerning whether "an antiretroviral agent" is "therapeutically effective" or "therapeutically ineffective." The following terms and phrases[1] remain at issue:

- "***therapeutically effective***" or "***therapeutically ineffective***": In May 1992, the only person that evaluated whether anti-HIV therapy for a patient is "therapeutically effective" or " ineffective" is the treating physician. The same is true today. One of ordinary skill in the art would consider these terms to refer to the medical effect intended by the treating physician for the particular treatment that is prescribed.
    - As described below, this Court should preclude Stanford from challenging Roche's construction of these terms because Stanford instructed its expert not to answer relevant questions at his August 19, 2007 deposition -- in violation of this Court's warnings and orders concerning depositions.

[1] Roche stipulates to Stanford's proposed construction of "statistically significant decline" and "collecting statistically significant data." Roche reserves its right to contend that such terms are fatally flawed under 35 U.S.C. § 112 and/or not infringed by Roche. For instance, Stanford's expert on the meaning of "statistically significant decline" could not, at deposition, answer the question as to how much of numerical decline would have been statistically significant to one of ordinary skill as of May 1992. Cannon Ex. A at Tr. 119-25.

- "***an antiretroviral agent***": Antiretroviral agents are drugs that are effective in reducing or stopping replication of retroviruses. The only drugs in this category that were known or available before 1995 were the nucleosides that inhibit reverse transcription. Not only does the law require terms to be given their meaning as of the time of invention, but the specification defines the term to be those antiretroviral agents "known" at the time.
- "***measuring the HIV RNA copy number***": this step, quantifying HIV copy number using PCR, should be limited to the techniques available to those of ordinary skill in the art as of May 1992. Stanford's claimed invention (a PCR assay) should not be construed to capture later arising technology such as real time PCR and internal standards, which Stanford neither invented nor taught in its patents.
- "testing" for "***presence***" or "***absence***" of "detectable HIV" using PCR: in direct contrast to the claims that include the "measuring step," the claims that require "testing" for the presence or absence of HIV RNA should be given their ordinary meaning -- i.e., a qualitative yes/no test based upon the lowest detection levels taught in the patent, 40 copies per 200 ul of sample.[2]

Patent law requires that claims be construed as they would have been understood by those of ordinary skill at the relevant time, in this case May 1992. As the Federal Circuit has held, claim construction is intended to define the invention in ways relevant to the infringement allegations and to provide meaning to a lay juror who may not be familiar with technical terms. The context for claim construction -- the interpretation of the metes and bounds of the invention -- includes the specification, prior art and the claims as a whole. Roche's claim constructions flow from this context -- exactly as the law requires. In contrast, Stanford's proposed constructions seek to remove the claim terms at issue from any context whatsoever -- in order to make the terms as malleable and open-ended as possible. To that end, in violation of Federal Circuit instruction, Stanford has avoided any mention of the accused products or accused activities.

The testimony of Drs. Bartlett and Lifson, along with prior art and literature from the relevant time period, is intended to provide the necessary context to the patent claims, including the background of HIV/AIDS; the development of HIV therapies; the role of the treating physician in evaluating and administering therapy; and the polymerase chain reaction ("PCR") assay; and the knowledge and understanding of those of ordinary skill in the field of the patents at the time of the filing of the original patent application in May 1992.

---

[2] Roche's position in the joint claim construction statement contained a typographical error. The detection level forth in the patent is 40 copies per 200 ul (microliter) of sample, not per ml.

I. STANFORD SHOULD BE PRECLUDED FROM CHALLENGING ROCHE'S DEFINITIONS OF " THERAPEUTICALLY EFFECTIVE" OR "THERAPEUTICALLY INEFFECTIVE" DUE TO ITS DISCOVERY ABUSES

In the Joint Claim Construction Statement, Stanford identified two experts, Paul Volberding and Fred Kramer, upon which it indicated it would rely for claim construction. Docket No. 172 and 172-6 ("Summary of Expert Opinions"). At the July 30, 2007 Claim Construction Prehearing Conference, Stanford asked this Court to order that no depositions of experts take place in connection with claim construction. Cannon Ex. B at Tr. 9:23 to 10:8. The Court ordered depositions to proceed. Id. On July 31, 2007 the parties entered into a formal stipulation regarding the expert deposition schedule, which the Court executed. Docket No. 175.

Despite this Court's order, on August 2, Stanford informed Roche that Stanford would not be submitting a declaration of Dr. Kramer in support of its ***opening*** claim construction brief (but may use him on reply) and would ***not*** be making him available for deposition on August 15, 2007 -- which precipitated Roche filing an emergency motion to enforce the Order concerning the deposition schedule. Docket Nos. 180 and 184. Counsel for Roche traveled to Boston (a location chosen to accommodate the witness) and appeared at the August 15, 2007 deposition; neither Stanford nor the witness appeared. Cannon Ex. C. Later on August 15, 2007, the Court ruled on Roche's emergency motion, stating: "If Stanford intends to rely on attestations, declarations or other statements of Fred Kramer in their reply, they shall make him available for deposition if requested by Roche. If they fail to make him available, they may not rely on him in their reply." Docket No. 186 at ¶ 2.[3] The Court also instructed the parties to "cooperate in all respects to fairly expedite the preparation and hearing of the upcoming matters." Id. at ¶ 3.

In support of its claim construction brief, Stanford offered the testimony of Dr. Paul Volberding. Docket No. 178. Dr. Volberding offered opinions about the meaning of the terms "therapeutically effective" and "therapeutically ineffective." Id. at ¶¶ 7-12. Dr. Volberding sat for

---

[3] Stanford chose to not make Dr. Kramer available, thus precluding him as a claim construction expert. Cannon Ex. D.

his deposition on Sunday, August 19, 2007, a day chosen to accommodate the witness' schedule. Docket No. 184-2.

Despite the witness being proffered as an independent expert and despite him offering opinions as to the meaning of the terms "therapeutically effective" and "therapeutically ineffective" in the context of evaluating anti-HIV therapy, counsel for Stanford thwarted the deposition of this witness by instructing the witness ***not to answer*** any of the following substantive questions.

> Q. When you get the results [of the viral load assay] back, does the lab make recommendations about the therapy for a particular patient?
>
> MS. RHYU: I instruct the witness not to answer because it's outside the scope of claim construction testimony.
>
> * * *
>
> Q. Dr. Volberding, when you get the results back from the lab, does the manufacturer of the test kit make recommendations about a patient's therapy?
>
> MS. RHYU: Same instruction.
> (Instruction not to answer.)
>
> * * *
>
> Q. When you get the results back from the lab, Dr. Volberding, does the manufacturer of the test kit make a determination about the effectiveness of the therapy for the particular patient?
>
> MS. RHYU: Same objection. . . . And instruction, sorry.
> (Instruction not to answer.)
>
> * * *
>
> Q. Does the lab that performed the assay make a conclusion about the effectiveness of therapy?
>
> MS. RHYU: I instruct the witness not to answer as being outside the scope of this deposition.
> (Instruction not to answer.)
>
> * * *
>
> Q. Does the manufacturer of the test kit make a conclusion about the effectiveness of therapy for a particular patient?
>
> MS. RHYU: Same instruction.
> (Instruction not to answer.)

Cannon Ex. A at Tr. 83:5 to 84:4; 84:6-10; 84:12-20; 87:21 to 88:2; and 88:6-8. The witness followed Stanford's counsel's instructions and did not answer the questions. Id.

There is no excuse for obstructing this witness's testimony. The questions go to the heart of these method claims. One hotly contested issue for claim construction in this case is ***who*** performs the assay and ***who*** makes evaluations about the effectiveness of therapy. For instance, to prove direct infringement, Stanford must prove that Roche performs each step of the assay. 35 U.S.C. § 271(a). To prove indirect infringement, Stanford must prove that Roche induces others to perform the steps, or contributes to that infringement consistent with 35 U.S.C. § 271(b), (c).

Not only is an instruction not to answer a substantive question wrong as a matter of principle, in this case, ***Stanford put into issue in its opening brief the question of who evaluates the effectiveness of therapy and in what way***. Docket No. 177 at page 3, lines 19-23 ("Some researchers looked at levels of molecules associated with immune system activation to gauge effectiveness of therapy" and "[i]nvestigators also attempted to evaluate the effectiveness of treatment by monitoring patient samples for their ability to induce infection in other cells").

Not only is ***who*** performs the methods a claim construction issue, it is an infringement issue, and it is entirely appropriate to raise issues related to infringement during claim construction. The Federal Circuit has recently instructed that the accused activities provide necessary context for claim construction:

> in reviewing claim construction in the context of infringement, the legal function of giving meaning to claim terms always takes place in the context of a specific accused infringing device or process. While a trial court should certainly not prejudge the ultimate infringement analysis by construing claims with an aim to include or exclude an accused product or process, knowledge of that product or process provides meaningful context for the first step of the infringement analysis, claim construction.

Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1326-27 (Fed. Cir. 2006). See also *Lava Trading, Inc. v. Sonic Trading Management, LLC*, 445 F.3d 1348 (Fed. Cir. 2006) (discussing the "vital contextual knowledge" of the accused activities for claim construction). In

fact, Stanford's brief is entirely devoid of information concerning Roche's alleged infringement -- a fatal flaw in Stanford's position.[4]

Stanford has done all it can to impede the deposition of its expert and undermine proper interpretation of these claims. Stanford should not be allowed to rely upon the declaration of Dr. Volberding in support of its claim construction positions as it prevented Dr. Volberding from answering relevant questions. Stanford should likewise be precluded from challenging Roche's construction of the terms "therapeutically effective" or "therapeutically ineffective." Roche's construction is fully consistent with the meaning of these claim terms, and this is an appropriate result given Stanford's discovery abuses.

II. LAW OF CLAIM CONSTRUCTION

It is a " bedrock principle" of patent law that " the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation omitted). The principles of claim construction that are most applicable to issues before this court are (1) claims are construed as they would have been understood at the time of the invention, i.e., there is a temporal context to claim construction, and claims cannot be literally construed to cover later developed technology that was not known or available to those of ordinary skill at the time of the invention; and (2) claims must be analyzed in light of the claims as a whole and the patent specification, of which the claims are a part.

"[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1313 (emphasis added). Thus, it is clear that patent claims have a "temporal" context, *Id.*, the meaning is fixed at a point in time.

---

[4] Stanford has refused to -- or cannot -- identify any specific instances of direct infringement of the patents despite a Roche interrogatory asking for this information. Cannon Ex. E at pp. 7-8 (May 29, 2007 Response to Interrogatory 32). Thus, despite this case being filed on October 14, 2005, almost two years later Stanford still cannot specify who, if anyone, actually infringes these patent claims and when and where any direct infringement occurred. This Court should not adopt Stanford's claim constructions given its refusal to provide appropriate context.

"[T]his court interprets the claim at issue to cover no more than what the specification supported at the time of filing." *Schering Corp. v. Amgen Inc*., 222 F.3d 1347, 1353 (Fed. Cir. 2000).

"Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips*, 415 F.3d at 1313. *See Netword, LLC v. Central Corp*., 242 F.3d 1347, 1352 (Fed.Cir.2001) ("The claims are directed to the invention that is described in the specification; they do not have meaning removed from the context from which they arose"). The claims themselves provide substantial guidance as to the meaning of particular claim terms. *Phillips*, 415 F.3d at 1314 (citing *ACTV, Inc. v. Walt Disney Co*., 346 F.3d 1082, 1088 (Fed.Cir.2003) ("the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms")).

III. BACKGROUND OF THE CLAIMED INVENTIONS

This background is drawn from the accompanying declarations of Dr. John G. Bartlett ("Bartlett ¶__") and Dr. Jeffrey D. Lifson ("Lifson ¶__"), as well as the publications attached and referenced in those declarations. Dr. Bartlett is an expert in the treatment of HIV patients. He is the former Chief of the Division of Infectious Diseases at The Johns Hopkins Hospital and Johns Hopkins University School of Medicine. He is the current Chief of Johns Hopkins AIDS Service. He is the co-chair of the Department of Health and Human Services panel that develops the federal "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" (http://AIDSinfo.nih.gov) and the author of the annually published book, MEDICAL MANAGEMENT OF HIV INFECTION (2007). Dr. Bartlett has personally treated patients infected with HIV since 1981 when this disease was first reported. Dr. Lifson is an expert in AIDS research and has been involved in such research since 1983. He is the Senior Principal Scientist and Head of the Retroviral and Pathogenesis Laboratory at the National Cancer Institute. As described in his declaration, a significant part of his research efforts and recognized expertise involve the development and application of assays, including the use of PCR, for monitoring the replication of HIV and related retroviruses.

A. **Treatment of HIV**

HIV is a lethal virus that attacks the cells of the human immune system. There is no known cure or vaccine. HIV eventually overwhelms the immune system, which leads progressively to a clinical condition known as AIDS (Acquired Immune Deficiency Syndrome). Destruction of the immune system and the development of AIDS leads to death, either from the disease itself or opportunistic infections that stem from immune failure. Bartlett ¶ 12.

Since late 1995, however, there has been a profound shift in the prospects for most patients in the United States. Improvement in patient outcome is primarily the result of improved drug therapies, including new antiretroviral agents unveiled in 1995 that, when used in combination with other antiretorviral drugs, suppress HIV's ability to replicate itself. The new therapies do not eradicate HIV and they are not without significant side effects, but they have led to an extraordinary change in the life expectancy for patients infected with HIV. Bartlett ¶ 13.

1. The Role of the Treating Physician

The treating physician cares for the patient and evaluates the patient's health, including the effectiveness of any therapy the patient may be taking. In 1992 and today, evaluation of a patient involves a wide variety of factors, including clinical symptoms, patient history and data from blood and other diagnostic tests. Ultimately, the treating physician's conclusions involve his or her professional medical judgment given the circumstances for each patient. Only the treating physician can prescribe antiretroviral agents for a patient. Bartlett ¶ 14.

2. History of the Disease

In 1981, a new disease was reported that would later be discovered to be AIDS caused by HIV. In 1983, researchers discovered the virus. HIV is a retrovirus. This means that its genetic code is in the form of single stranded RNA (unlike double stranded DNA). In 1985, the first test was developed that detected HIV in blood. At this time there was active research into the replication cycle of HIV. Bartlett ¶ 15-17.

The virus is a particle that is coated with unique proteins -- these proteins fuse to CD4 proteins, which are proteins on the surface of the cells of the immune system. Once fused, the contents of the virus particle are released into the human cell. The HIV RNA is then "***reverse***

transcribed" to become DNA. The resulting HIV DNA is then ***integrated*** into the chromosome of the host cell. After a period of time, the HIV DNA is then activated within the host DNA and begins to express itself. The results of the expression of the HIV DNA are the building blocks of new HIV virus particles. These building blocks are then assembled by a protein called ***protease*** into virus particles that are released to infect new cells. Bartlett ¶ 18. Attached as Exhibit B to Dr. Bartlett's declaration is an article that he co-authored in SCIENTIFIC AMERICAN in 1998 that describes and illustrates this process in more detail.

Since the advent of HIV and continuing through today, there has been active research to identify potential drugs that could block, suppress or slow down the progressive nature of the disease. Some of the early efforts included identification of potential drugs that would interfere with the replication process of the virus. Bartlett ¶ 19.

In 1986, researchers conducted the first clinical trial of a drug -- zidovudine or AZT -- that would block the reverse transcription step of the HIV replication cycle. In 1987, the FDA approved AZT for the treatment of patients. Although AZT delayed the progression of the disease, the nature of HIV prevented AZT from providing long term benefits. This is because the genetic code of HIV rapidly mutates and develops resistance to drugs. Eventually, HIV overwhelms the cells of the immune system. Bartlett ¶¶ 20-21

As mentioned above, cells of the body's immune system contain CD4 proteins. For most diseases, CD4 proteins help the body's immune system identify and destroy pathogens such as a virus. The measure of a person's CD4 cell count is a measure of the robustness of that person's immune system. For normal people, doctors expect a CD4 count of 800 to 1050 cells per ml. The condition of AIDS is defined by a number of diagnostic measurements, including a CD4 count of less than 200 cells per milliter of blood. Thus, when a patient has a CD4 count of less than 200, he or she is said to have AIDS. It is a goal of a treating physician in 1992 and today to make sure a patient's CD4 count is as high as possible. Bartlett ¶ 22.

The relationship between CD4 count and the levels of HIV virus particles in the blood ("viral load") is complex and has been the subject of active research. Today, it is generally accepted that viral load cannot be correlated with CD4 cell count. A treating physician of ordinary

skill in 1992 and today would always measure CD4 cell count independent of any viral load measurement because only the CD4 cell count provides direct information about the level of a patient's immune system. Indeed, the baseline or pre-treatment HIV viral load is not very important in deciding when to treat HIV. The CD4 count dictates that decision. Bartlett ¶ 23.

3. Clinical Trials

There have been many potential drugs identified to suppress HIV. Only a very few have survived the clinical trial process and been found to have clinical value as therapy for the treatment of HIV infected patients. Clinical trials are, by definition, research. The investigator obtains informed consent from each individual involved in the trial. One aspect of a clinical trial is to give one population a proposed drug regimen and another population a different drug regimen. Only after what are called Phase III clinical trials are drugs approved by the FDA and made available for prescription and therefore can be used as therapy. Bartlett ¶ 24.

The results of clinical trials are not generally known to AIDS doctors and HIV researchers as the trials are ongoing. Often, the results of trials are presented at annual conferences shortly before FDA approval. For instance, the results of the protease inhibitor trials were presented in a conference in 1995, and the FDA approved the protease inhibitor Squinavir in December 1995. Bartlett ¶ 25.

4. Dramatic New Drugs Unveiled In 1995-96

In late 1995, researchers presented dramatic data from clinical trials of protease inhibitors and novel combinations of drugs -- drug regimens that would be come to be known as HAART ("Highly Active Antiretroviral Therapy"). Doctors soon realized that a profound shift had taken place. As a result of these new drugs, the mortality rate for patients in the United States plummeted. At the ten year anniversary of HAART in 2005, many articles were written that described the sea change with the new drugs. An example of such an article is by Stanford's expert witness Dr. Paul Volberding, describing the "truly major breakthrough in anti-HIV therapy" that was "unveiled in early 1996." See Exhibit C to Dr. Bartlett's declaration.

Although the drugs unveiled in 1995 and 1996 were a breakthrough, significant issues remain. The drugs have significant side effects and can be toxic. Due to the levels of drugs

required to be taken, and the complexity of the combinations of pills that must be ingested each day, many patients have difficulty adhering to the regimen. In 1992 and today, there are many options for a treating physician, and each patient must be evaluated on an individual basis. What works for one patient may not work for another. Bartlett ¶ 27.

Physicians must choose what combinations of drugs are appropriate for a given patient to address all the relevant issues. The treating physician analyzes the following factors in determining what drug regimen to give to the patient: (a) baseline resistance of the patient's HIV strain (different for every patient); (b) Side effects of the drug; (c) concurrent conditions (pregnancy, kidney failure, hepatitis B, heart disease, elevated cholesterol and prior exposure to all antiretroviral drugs); and (d) patient preference (one pill per day, no big pills, etc). Every one of these factors impacts the treatment. Bartlett ¶ 27.

In 1992, as today, a treating physician defines success by clinical outcome. Today, the goal is to have an appropriate CD4 count, viral load below 50 copies per ml, and appropriate tolerance. The degree of decline of viral load is not a measure of effectiveness. Bartlett ¶ 28.

B. **Background To PCR Assays**

1. PCR

As the Court described in its April 16, 2007 Summary Judgment ("SJ") Order, scientists at Cetus Corporation in the mid 1980s developed PCR, a method to amplify and produce large amounts of specific target DNA sequences. Docket No. 157 at p. 3. . PCR is a tool that has had great impact on molecular biology. Cetus scientist Dr. Kary Mullis was awarded the Nobel Prize in Chemistry in 1993 for his PCR work. Docket No. 157 at p. 3; Lifson ¶ 6. To conduct the PCR, a scientist assembles a reaction mixture that includes the target DNA. The target DNA is the original template from which all copies are derived. Lifson ¶ 8-9. Attached to Dr. Lifson's declaration at Exhibit C is an article from 1990 that sets forth the basic PCR mixture and reaction sequence.

Dr. Lifson's declaration describes the three step process of denaturation, annealing, and extension that forms one "cycle" of PCR. After completion of this process, for each starting copy of target sequence, there should be two copies that are *replicas* of the original target

sequence. Because the primers and DNA polymerase enzyme create an replica of the original target DNA sequence during each amplification cycle, each new replica sequence can serve as a template for production of more replica sequences. Thus, each cycle amplifies the amount of the desired DNA sequence in an exponential fashion. The more cycles of amplification that are conducted, the more product is generated. Lifson ¶¶ 10-11.

As discussed below, the cycle number in the claimed method of the patents in suit is "about 30 cycles" -- meaning that a scientist conducts PCR for about 30 cycles and then works with the end product of those cycles. This type of PCR method -- running a PCR for a particular number of cycles and then measuring the result -- is known as "end point PCR". Lifson ¶ 11.

PCR amplifies a defined target sequence of double stranded DNA. However, RNA is another molecule that contains genetic information -- but it is single stranded. To apply PCR to RNA target sequences, the RNA must be converted to DNA. To do this, the scientist must perform a "reverse transcription" reaction on the RNA to create a complementary DNA copy or cDNA. This is called RT-PCR. See Lifson ¶ 12 and Lifson Ex. D.

With the development of PCR, scientists sought to apply the new technique to a variety of new targets related to clinically significant conditions and diseases, such as HIV infection. *See* Lifson ¶ 13 and Lifson Ex. E. See also SJ Order at p. 3 (In 1985, Cetus began looking for ways to use PCR to detect and quantify the presence of HIV in blood.") (citing Declaration of John J. Sninsky, ¶¶ 5-9, Docket No. 82-1).

PCR technology has undergone dramatic changes and improvements since it was first developed. What one of skill in the art today would understand by a method claiming a PCR reaction is different now than it would have been in May 1992. The advance of "real time" PCR is discussed below. Lifson ¶ 14.

2. Quantitative PCR

In the early 1990's, HIV researchers were developing methods for quantitative measurement of HIV to enable monitoring of responses to antiviral treatment. Indeed, as Stanford's expert Dr. Volberding confirmed in an article he co-authored, "early studies demonstrated a clear association between the titer of culturable virus in the plasma and the clinical

stage of disease." Cannon Ex. K and Cannon Ex A, 89-90. The "early studies" referenced in Dr. Volberding's article are from 1989 and 1991, all predating the May 1992 filing of the patent. See also Sninsky and Kwok, 1990, Lifson ¶ 19 and Lifson Ex. E at 262 ("experiments on the quantitation of PCR product suggest that the procedure could be used for the monitoring of viral load in patients receiving therapeutic agents").

One approach in the art at the time was known as competitive PCR. Lifson Ex. F. A similar approach was developed by Cetus scientist Alice Wang and her colleagues, also for measurement of mRNA. Lifson Exs. G and H. Lifson ¶¶ 20-22.

3. 1991 JID Paper

In 1991, Stanford's Mark Holodniy and Thomas Merigan, along with Cetus scientist Alice Wang and others co-authored "Detection and Quantitation of Human Immunodeficiency Virus RNA in Patient Serum by Use of the Polymerase Chain Reaction," THE JOURNAL OF INFECTIOUS DISEASES, 163:862-866 (April 1991) ("JID paper"). See Lifson Ex. I.

This JID paper uses a five step procedure including end point PCR to quantify HIV copy number from a patient sample, such as a plasma or serum specimen.

i. First, RNA is extracted from the patient sample ("extraction");

ii. Second, RNA is reverse transcribed ("reverse transcription");

iii. Third, PCR "amplification" is carried out for 30 cycles;;

iv. Fourth, the PCR product is captured and detected using a horseradish peroxidase (HRP) labeled probe and a colorimetric reaction - a color intensity depending upon the amount of PCR product ("detection"); and

v. Fifth, quantification is accomplished by constructing a standard curve of color intensities from a dilution series of known copy numbers of a RNA standard derived from the HIV *gag* gene ("quantification") and comparing the unknown value to this standard curve.

Lifson ¶¶ 23-26. This Court's SJ Order further described the five step assay developed at Cetus. Docket No. 157 at pp. 7-8.

With respect to the sensitivity of the assay described in the JID paper, the authors define the average background optical density and report a detection level for this assay of 40 copies per 200 microliters (a unit of volume) of extracted plasma or serum. Lifson ¶ 26.

The JID paper concludes that: "virion HIV RNA was detected and quantitated in the serum of HIV-positive patients by PCR" and that: "Serum PCR may provide an additional marker of disease progression and drug efficacy that could improve our ability to monitor the course of HIV infection." Lifson Ex. I.

4. Development of Real Time PCR[5]

A major advance subsequent to May 1992 involved the development of kinetic procedures for quantitative PCR, designated "real time PCR methods". The key feature of such methods is measuring accumulation of amplified product to monitor the ongoing PCR reaction kinetically, in real time. In real time methods, quantification is based not on the amount of amplified PCR product produced after a set number of cycles, but rather how many amplification cycles are required to first generate a quantifiable (above background) amount of amplified product. Thus, in contrast to end point PCR, real time PCR produces results as the cycles are ongoing. Real time PCR, which is based on a kinetic measurement principle and uses different detection probes and reagents than end point PCR, represents a qualitatively different approach to quantitative PCR relative to endpoint PCR based assays. Lifson ¶ 28.

Dr. Lifson has identified the earliest real time quantitation PCR assay of which he is aware and it was published in 1993, after the filing of the patents in suit. See Lifson ¶ 29 and Lifson Ex. J. Furthermore, in 1996, an improved approach for using real time PCR methods for quantitative RT PCR applications was developed for quantitating RNA. Lifson ¶ 30 and Lifson Ex. K.

---

[5] The accused products in this case are Roche's AMPLICOR HIV test kits, which all use end point PCR -- as set forth in Stanford's April 13, 2007 infringement contentions. However, Roche has been selling in Europe since December 2003 a next generation of HIV kits that use real time PCR. These real time PCR kits have undergone clinical trials in the United States and on May 11, 2007 the FDA approved these real time PCR kits for use in the United States. The real time kits are not accused products, and Stanford has not sought leave to amend its infringement contentions as it is required to do under the Patent Local Rules. To the extent Stanford in the future may seek leave to amend its infringement contentions (which Roche will object to as untimely as real time PCR HIV products have been known to Stanford long before it filed its infringement contentions), Roche believes it is appropriate for the Court to interpret the claims with respect to real time PCR.

IV. PATENTS IN SUIT

Stanford filed the original application for the patents in suit in May 1992. The three patents in share the same named inventors (Thomas Merigan, David Katzenstein and Mark Holodniy) and same specification. *See* Cannon Exs. F, G, H. For ease of reference, the brief will refer to the specification of the '730 patent, which was the first to issue.

As the title of the each of the three patents makes clear, the patents concern PCR assays and medical decisions: "Polymerase Chain Reaction Assays For Monitoring Antitretroviral Therapy And Making Therapeutic Decisions In The Treatment Of Acquired Immunodeficiency Syndrome."

1. Specification

The specification of the patents in suit contains two separate technical disclosures. The first is a description of a test to detect a mutation in codon 215 of HIV genetic code. *See* Cannon Ex. F at col. 2, lines 26-63. This and related portions of the disclosure do not relate to the claims at issue and are the subject of other patents with an additional named inventor (Michael Kozal) not asserted in this case. The relevant portion of the patent specification describes measuring "viral load" and the alleged discovery by the inventors that HIV RNA copy number may be measured by PCR and used to monitor the effectiveness of therapy. Id., col 2, lines 15-26.

The patent describes using PCR to quantify viral load in two places: the "Detailed Description" beginning at column 4, line 1 ("PCR Assay of Plasma HIV RNA") and "Example 6" beginning at column 9 ("Example: Reduction in Plasma Human Immunodeficiency Virus Ribonucleic Acid After Dideoxynucleoside Therapy As Determined By The Polymerase Chain Reaction"). As Dr. Lifson explains, however, the '730 patent specification describes exactly the five-step assay set forth in the prior art JID article: (1) extraction; (2) reverse transcription; (3) amplification; (4) detection and (5) quantification. Indeed, with respect to the critical step of quantifying viral load, the patent specification simply references the JID paper:

	1991 JID Paper	*'730 Patent: Cols 4-5*	*'730 Patent: Cols. 9-10*
1. Extraction	"Total RNA from 200 µl of serum was extracted using guanidinium thiocynate"	"RNA may be extracted from plasma using standard techniques . . . for example 200 µl of clarified plasma to which 200 µl of 5M guanidinium thiocynate had previously been added": lines 11-16	"RNA was extracted from plasma using standard techniques . . . for example 200 µl of clarified plasma to which 200 µl of 5M guanidinium thiocynate had previously been added": col. 9, lines 63-66
2. Reverse Transcription	"reverse transcribed with M-MLV reverse transcriptase" [Note: M-MLV refers to Moloney murine leukemia virus]	"From plasma RNA, HIV RNA may be transcribed to cDNA using a suitable reverse transcriptase (for example Moloney murine leukemia virus reverse transciptase)": lines 21-23	"HIV RNA was transcribed to cDNA using Moloney murine leukemia virus reverse transciptase": col. 10, lines 5-6
3. Amplification	"PCR was carried out . . . for 30 cycles of amplification in a DNA thermal cycler (Perkin Elmer Cetus)"	"tubes containing the reaction may be placed in a DNA thermal cycler (e.g., Perkin Elmer Cetus) for about 30 cycles of amplification": lines 39-42	"Tubes were placed in a DNA thermal cycler (Perkin Elmer Cetus) for 30 cycles of amplification": col 10, lines 26-27.
4. Detection	SK19 probe labeled with HRP for enzyme linked affinity assay read at 490 nm	In a preferred embodiment, "probe may be labeled with horseradish peroxidase (HRP) and copy number may be evaluated by an enzyme linked affinity assay . . . measured at 490 nm": lines 64-67 and col. 5, lines 27-28	"Enzyme linked affinity assay . . . measured at 490 nm": col 10, lines 33 and 58. The probe used was "SK19" labeled with "horseradish peroxidase (HRP)"
5. Quantification	External standard curve with cRNA *gag* gene standard of known copy number	"Copy number from subject samples may be determined from the absorbances obtained from a dilution series of an RNA gag gene construct of known copy number. (Holodniy et al., 1991, J. Infect. Dis. 163:862-866)": col. 5, lines 32-36.	"Copy number from subject samples may be determined from the absorbances obtained from a dilution series of an RNA gag gene construct of known copy number. (Holodniy et al., 1991, J. Infect. Dis. 163:862-866)":

In addition, in the JID paper and the example and description in the patent, the cRNA standard used to generate the standard curve is "external." This means the standard is amplified in a separate tube from the unknown. Lifson ¶ 41. Indeed, in a paper published in 1994, one of the named inventors, Mark Holodniy, explained that with respect to PCR HIV quantification, he had developed an external standard and that an external standard could be advantageous:

> "An external RNA control was described by our group, which utilizes a *gag* gene RNA standard constructed from a plasmid with a T7 promoter and *gag* gene insert. This external control is utilized in a separate reaction series that employs the same gag gene primer pair used for the patient sample RT-PCR reaction. . . . The advantage of such a system revolves around the fact that one patient sample in duplicate or triplicate can be assayed with an entire external standard curve."

Cannon Ex. I at p. 339 (Mark Holodniy, "Clinical Application of Reverse Transcription Polymerase Chain Reaction for HIV Infection," in CLINICS IN LABORATORY MEDICINE, Vol. 14: 335-349 (June 1994) (citing JID Article).[6]

In addition, as can be seen from the patent and Dr. Lifson's explanation, the assay described in the patent is reported to have the same detection level as that set forth in the 1991 JID paper: an absorbance of 0.135, corresponding to 40 HIV RNA copies per 200 µl [microliters -- a unit of volume] of sample. See Cannon Ex. F, Col. 10, lines 59-67; col. 12, lines 51-52.

2. Claims

Each of the claims of the three patents is a method of evaluating the effectiveness of anti-HIV therapy of a patient by performing a particular PCR assay. There are two types of method claims in these patents. The first type includes a step for "measuring" the HIV copy number. See '730 patent, claims 9, 14 and 19 and '705 patent claims 1 and 8. For instance, claim 9 of the '730 patent reads with emphasis on the disputed terms:

> 9. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising
>
> (i) collecting a plasma sample from an HIV-infected patient who is being treated with ***an antiretroviral agent***;
>
> (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and
>
> (iii) ***measuring the HIV RNA copy number*** using the product of the PCR, in which an HIV RNA copy number greater than about 500 per 200 ul of plasma correlates positively with ***the conclusion that the antiretroviral agent is therapeutically ineffective***.

---

[6] For purposes of claim construction, the significance of the standard being external, and techniques for HIV PCR quantification being limited to external standards at the time, is that later developed technology led to internal standards that could be amplified in the same tube as the unknown.

Cannon Ex. F. Similarly, Claim 1 of the '705 patent reads with emphasis:

> 1. A method of evaluating the effectiveness of anti-HIV therapy of an HIV-infected patient comprising:
>
> a) collecting statistically significant data useful for determining whether or not a decline in plasma HIV RNA copy numbers exists after initiating treatment of an HIV-infected patient with ***an antiretroviral agent*** by:
>
> (i) collecting more than one plasma sample from the HIV-infected patient at time intervals sufficient to ascertain the existence of a statistically significant decline in plasma HIV RNA copy numbers;
>
> (ii) amplifying the HIV-encoding nucleic acid in the plasma samples using HIV primers via PCR for about 30 cycles;
>
> (iii) ***measuring HIV RNA copy numbers*** using the products of the PCR of step (ii);
>
> (iv) comparing the HIV RNA copy numbers in the plasma samples collected during the treatment; and
>
> b) evaluating whether a statistically significant decline in plasma HIV RNA copy numbers exists in evaluating the effectiveness of anti-HIV therapy of a patient.

Cannon Ex. G.

Other method claims do not include a "measuring step, but instead include a step for "testing" for the "presence" or "absence" of detectable HIV-encoding nucleic acid. See '730 Patent, claims 1, 6, 7, 8 and '041 Patent, claims 1, 2, 3, Cannon Exs. G and H. For instance, Claims 1 and 2 of the '041 patent read with emphasis:

> 1. A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising:
>
> correlating the ***presence or absence of detectable HIV-encoding nucleic acid*** in a plasma sample of an HIV infected patient with an absolute CD4 count, wherein the presence or absence of said detectable HIV-encoding nucleic acid is determined by
>
> (i) collecting a plasma samples from an HIV-infected patient who is being treated with ***an antiretroviral agent***;
>
> (ii) amplifying HIV-encoding nucleic acid that may be present in the plasma sample using HIV primers via PCR and;
>
> (iii) ***testing for the presence of HIV-encoding nucleic acid sequence in the product of the PCR***.

> 2. The method of claim 1, wherein the ***absence*** of HIV-encoding nucleic acid and the absolute CD4 count being greater than about 200 cells per cubic millimeter correlate positively with ***the conclusion that the antiretroviral agent is therapeutically effective***.

V. LEVEL OF ORDINARY SKILL

The patents at issue all claim a PCR assay used to generate data for the purpose of evaluating the effectiveness of anti-HIV therapy and reaching a conclusion about whether therapy was effective or not. As Dr. Bartlett describes, and Dr. Lifson agrees, in 1992, as is the case today, only a treating physician evaluates his or her patient and the effectiveness of therapy. Bartlett ¶ 29; Lifson ¶ 31.

With respect to the development and use of PCR techniques, a person of ordinary skill in this art would have a medical degree or graduate degree in biochemistry or a related field and at least two years of relevant laboratory bench experience conducting PCR assays. See Lifson ¶ 32; Bartlett ¶ 30. Stanford's definition is too open-ended and makes no reference to PCR skills. The assay in question is a PCR assay, and even though PCR was relatively new in the early 1990s, one of ordinary skill in the art relating to PCR assays should have experience and success in conducting such assays.

VI. CLAIM CONSTRUCTION

A. "Therapeutically effective" and "therapeutically ineffective"

- Roche's Construction: "elicits the medical effect intended by the treating physician such that the course of treatment is (or is not) modified."

Reading the claims as a whole, evaluation as to whether treatment is "therapeutically effective" or "therapeutically ineffective" is a medical decision. Indeed the title of each of the patents refers to "Making Therapeutic Decisions In The Treatment Of Acquired Immunodeficiency Syndrome." Cannon Ex. F (emphasis added). Only a doctor can make medical decisions. In addition, a medical dictionary from the relevant time defines "effectiveness" to be: "The ability to cause the expected or intended effect or result." Cannon Ex. J at p. 608. Again, only a doctor can evaluate the expected or intended result.

As Dr. Bartlett explains, in the context of these patents as of May 1992, one of ordinary skill in the art would consider "therapeutically effective" or "therapeutically ineffective" to be the medical effect intended by the treating physician for the particular treatment that is prescribed for the patient. A conclusion about the effectiveness or ineffectiveness of the therapy would be coupled with a decision by the treating physician as to whether or not to modify the treatment. Bartlett ¶ 36.

The patent specification provides no guidance as to what outcomes are "therapeutically effective" or "therapeutically ineffective." Accordingly, one of skill in the art in treating HIV patients must exercise his or her professional medical judgment.

The Stanford patents contrast with those construed in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, *rehearing denied*, 469 F.3d 1039 (Fed. Cir. 2006). In *Amgen*, the Federal Circuit construed "therapeutically effective amount" to be an amount "that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification." 457 F.3d at 1303. The difference between *Amgen* and the present case is that the *Amgen* patent specifically listed the medical effects that were intended. *Id.*; *see* U.S. Patent No. 5,955,422, col. 33, ll. 16-22. The patents here do not. Rather, the patents state that: "If a patient being treated with an antiretroviral therapeutic agent exhibits an increase in plasma HIV RNA copy number, *a physician should consider* altering the patients treatment regimen." Cannon Ex. F at col. 2, lines. 45-49 (emphasis added). Thus, the only measure of therapeutic effectiveness, according to the patent specification, is whether the physician should consider altering the treatment regimen. The physician's *intended* effect, and the doctor's mental consideration of whether therapy should be changed, is the only indication of effectiveness provided by the specification.

Stanford argues that such a construction improperly injects a mental medical decision into the claims terms -- but it is Stanford that wrote the claims. And it is Stanford's specification that provides absolutely no guidance as to what result is therapeutically effective or not. Stanford's expert has not testified to the contrary. Dr. Volberding states that: "Persons of ordinary skill have a general understanding of effectiveness of a therapy as working against HIV."

Decl. of Paul Volberding, Docket No. 178, ¶ 9. This only begs the question of *who* determines whether a therapy is "working," and *how* that assessment is made; the answer is a physician using his or her medical judgment. Thus, given the claim language and lack of any guideposts as to effectiveness, the patent offers no choice other than a physician's conclusion about whether a therapy regimen is "therapeutically effective" or not.

B. "Antiretroviral agent"

- Roche's Construction: "antiretroviral agents available to doctors for the treatment of AIDS/HIV infected patients in 1992."

Each claim of the patents includes the term "an antiretroviral agent." The specification defines: "Antiretroviral agent, as used herein, include any *known* antiretroviral agent." Cannon Ex. F at col. 8, lines 39-40 (emphasis added).

The word "known" is phrased in the past tense and is expressly confined to *known* antiretroviral agents when the specification was written, *i.e.* May 14, 1992. *Kopykake Enterprises, Inc. v. Lucks Co.*, 264 F.3d 1377, 1382-83 (Fed. Cir. 2001) is on point. In *Kopykake*, the court held that "conventional" in a specification definition means "conventional at the time of invention." Temporally, "known" and "conventional" both convey the same past-tense limitation.

Stanford's citation to *SuperGuide Corp. v. DirecTV Enterprises*, 358 F.3d 870 (Fed. Cir. 2004) does not support its position. To the contrary, *SuperGuide* supports Roche's position. In *SuperGuide*, the dispute concerned whether "regularly received television signals" covered digital signals or were limited to analog signals. *Id.* at 876. Importantly, digital signals were not new: they were known and enabled to those of ordinary skill in the art at the time of filing. *Id.* at 879 ("those skilled in the art knew of the existence of digital video data at the time"). Indeed, the patentee described digital signals in the specification. *Id.* at 879-80. The only argument was that digital signals were not *actually* broadcast even though people knew about them. *Id.* at 878. The Federal Circuit declined to limit the claim to what was actually broadcast for mass consumption at the time, but instead extended it to cover what was known and available to skilled artisans with knowledge—the relevant audience for a patent. The court made clear that "those skilled in the art knew both formats could be used for video." *SuperGuide*, 358 F.3d at

880. In contrast to the situation in SuperGuide, as of May 1992, only a limited number of drugs were known or available for HIV therapy.

Dr. Bartlett explains that, in general, antiretroviral agents are drugs that are effective in reducing or stopping replication of retroviruses. However, the only drugs in this category that were known or available before 1995 were the nucleosides that inhibit reverse transcription. Bartlett ¶¶ 38-41.

Stanford's position is that because some of the later drugs may have been in clinical trials in 1992 (though Stanford offers no evidence of this), they were somehow "known" or available to those of skill in the art. Not so. First, clinical trials are, by definition, research. The results of clinical trials are not known until the trials are complete -- only then do investigators know whether a drug will work for therapy of a patient. Second, clinical trials are not public endeavors. Even Stanford's expert Dr. Volberding admitted that he (and other investigators) learned of the results of the protease inhibitor trials "for the first time" when they were presented at a scientific conference in 1995-6, shortly before FDA approval. Cannon Ex. A Tr. 60-61.

Thus, protease inhibitors and HAART therapy were neither known nor available for therapy until well after May 1992. Bartlett ¶¶ 38-41. These drugs were first made known to the HIV research community in conferences in late 1995 and early 1996. Id. As such, the literal definition of antiretroviral drugs used in the claims cannot include these later developed therapies because these were not known to those of ordinary skill or available to be used as therapy by those of ordinary skill "at the time of the invention." *Phillips*, 415 F.3d at 1313.

C. "measuring HIV RNA copy numbers"

- Roche's Construction: "techniques available in May 1992 to quantify HIV RNA copy number using PCR, specifically the assay in the 1991 JID article as set forth in the specification."

One of ordinary skill in the art as of May 1992 would interpret the "measuring" steps of the '730 patent and '705 patent to be directed to using PCR to quantify the HIV RNA copy number. As explained by Dr. Lifson, the available techniques for HIV quantification at the time, however, were limited. Lifson ¶¶ 43-46.

The specification describes in two places a procedure to quantify HIV RNA copy number: column 4 in the "Detailed Description" and columns 9-10 in "Example 6." These descriptions are both the five-step end point PCR assay set forth in the 1991 JID paper co-authored by Stanford and Cetus scientists. The patent enables no more than the assay taught in the JID paper, and Stanford should not be able to claim as its invention any more than it enables: "The scope of the claims must be less than or equal to the scope of the enablement." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999).

Thus, one of skill in the art of PCR techniques would have understood the quantification steps to refer to the skills and techniques available for HIV quantification described in the patent and then available art -- specifically the HIV standards and methods then available and/or described for quantification. This means end point PCR. As further evidence that the claims mean end point PCR, all of the claims refer to 30 cycles of PCR. As Dr. Lifson explains, a reference to a set number of cycles indicates to one of skill in the art that the scientist is to perform the specified number of cycles and then examine a portion of the amplified PCR product at the completion of the amplification. Lifson ¶ 44.

The claims should not be construed literally to include real time PCR or internal standards because it cannot be disputed that these are after-developed technologies for HIV RNA quantification. Lifson ¶ 46.

D. "Testing for the presence" or "absence"

- Roche's Construction: "qualitative result indicating greater than or less than 40 copies of HIV RNA per 200 ul of sample."

The claims of the patents in suit are either (a) "measuring HIV RNA copy number claims or (b) testing for the "presence" or "absence" claims. There is no dispute that the measuring step refers to quantification of viral load. Stanford, however, argues that the presence/absence claims also refer to quantification. Not so.

First, the plain meaning of presence/absence indicates a yes/no test. Determining whether a compound is present or not is fundamentally different from measuring how much is there. Indeed, Stanford uses different terms in different claims. Stanford's argument that the

terms "presence," "absence" and "detectable" really mean "measuring" instead violates the principle that "[w]hen different words or phrases are used in separate claims, a difference in meaning is presumed." *Nystrom v. Trex Co.*, 424 F.3d 1136, 1143 (Fed. Cir. 2005).

When Stanford wanted to make clear in the claims that the method involved quantification, it did so, by using the phrase "measuring the HIV RNA copy number." Stanford did not define "presence," "absence," or "detectable" in the specification.

Stanford also relies on its statements to the PTO regarding quantitation. A patentee's reliance on his *own* statements to the PTO is entitled to virtually no weight in the claim construction process, even if the intent to broaden the claim is unambiguous. *Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1319 (Fed. Cir. 2006) ("even if we were to agree with Honeywell that the patentee clearly expressed his intention during prosecution to have the "fuel injection system component" limitation include components in addition to a fuel filter, it would not change the result in this case").

Finally, because presence/absence is not defined, Stanford should be limited to the detection levels it described as providing the results it relied upon: 40 copies per 200 ul of sample. See Lifson ¶ 42. The claims should not be construed to be broader than what Stanford actually enabled.

DATED: August 29, 2007

Respectfully submitted,

PRUETZ LAW GROUP LLP

QUINN EMANUEL URQUHART OLIVER & HEDGES, LLP

By /s/
Brian C. Cannon
Attorneys for Defendants and Counterclaimants Roche Molecular Systems, Inc.; Roche Diagnostics Corporation; and Roche Diagnostics Operations, Inc.