Petition to

The Honorable Bill Richardson
Secretary of Energy
Washington, D.C. 20585

Concerning the Waiver of Government Rights to Certain Inventions Related to In-Situ Hybridization Technology Developed Under Contract No. W-7405-ENG-48 With the University of California for Operation of the Lawrence Livermore National Laboratory

Date: **June 22, 1999**

Petitioner:

Ventana Medical Systems, Inc.
Tucson, Arizona

Daniel Pinkel as co-inventors. The application, entitled "Methods and Compositions for Chromosome-Specific Staining," broadly claimed (1) any and all methods of staining chromosomes by ISH, and (2) any and all probes substantially free of repetitive sequences for staining chromosomes. (See claims 1, 17, Exhibit 2)

At that time the University was required to assign title to the Government of any invention made under the contract unless it favorably petitions the DOE to waive the Government's rights to the invention. This practice was in accord with law and regulations that requires title to vest in the United States for inventions made under a DOE contract unless the agency waives the Government's rights to such inventions based on a determination that the interests of the United States and the general public will be best served by such a waiver. (42 U.S.C. §5908; See also, Federal Procurement Regulations 41 CFR 1-9.107 et seq.)

Thus, because the inventions were made while performing under the DOE contract, the inventions would have been owned by the government absent a written waiver of those rights. On June 30, 1986 the University petitioned the DOE to obtain such a waiver with respect to the inventions covered in the 819,314 application. (Exhibit 3a). In support of its Petition, answers to the following questions were submitted.

2. *Give a brief description of the subject invention.*

A method is disclosed for detecting chromosomal translocations and trisomies and is based on the use of chromosome specific recombinant DNA probes. Multiple chromosomes specific probes are fluorescently labeled and hybridized to a cell and/or chromosomes. Specifically, to detect trisomy, if the fetus is normal, all cells are equally fluorescent. If the fetus is carrying a trisomy, the fetal cells will be 50 percent more fluorescent than the maternal cells.

10. *What will be the effect on competition and market concentration if the above requested waiver is granted? Would the acquisition of the waiver of rights requested be likely to place the Petitioner in a preferred or dominant position in this field? Give reasons for your conclusions.*

> Petitioner is not a manufacturer. Its position would be "dominant" only to the extent that it would hold the patent rights for the express purpose of licensing them for commercial development and use.
>
> Successful development of the invention will result in expanded business opportunities for industrial concerns and ultimate public benefit.
>
> Such anticipated results are consonant with the policy and objectives of Congress in its enactment of public law 96-517 to use the patent system to promote the utilization of inventions arising from federally supported research and development, to promote collaboration between commercial concerns and universities, and to insure that inventions made by non profit organizations are used in a manner to promote free competition and enterprise toward commercialization and public availability of such interest will result from the granting of the waiver of rights in this invention. (emphasis added)

On August 14, 1986 the University submitted a second Petition to the DOE. (Exhibit 3b) The Petition sought a waiver of government of rights to the invention in U.S. Patent Application Serial No. 937,793 which was later filed on December 24, 1986 as a continuation-in-part (C-I-P) of the 819,314 application. The C-I-P application had claims similar in scope to those in the earlier application directed to (1) any and all methods of staining chromosomal DNA by ISH, and (2) any and all probes substantially free of repetitive sequences for staining chromosomes.

In support of its Petition, the University described the invention as follows:

> A method is provided for producing single-stranded nucleic-acid probes with no self-complementary sequences, and for treating target DNAs for use therewith, such that only single-stranded sequences complementary to probe sequences are available for hybridization. The method significantly increases the efficiency of hybridization mixtures by increasing effective probe concentration by eliminating self-hybridization between both probe and target DNAs, and by reducing the amount of target DNA available for mismatched hybridizations.

The University answered the competition question as they had in the first Petition, that they would use the intellectual property to "promote free competition" and would seek "public availability." In neither Petition does the University indicate that the patent applications broadly claim staining chromosomal DNA by ISH.

On May 7, 1987 DOE officials favorably reviewed the University's first Petition and recommended that the Government's patent rights be waived with respect to the "invention directed to recombinant DNA procedures for detection of chromosomal translocations and trisomies" as covered by the 819,314 patent application (Exhibit 4a). In making its decision, the DOE reviewers stated that they were assuming as follows:

> Granting the waiver should not have an undesirable effect on competition or market concentration since the invention has relatively specialized applications. Additionally, Petitioner will be a licensor with a direct interest in obtaining widespread commercialization.

On July 6, 1987 DOE officials also recommended granting the University's second petition and waiving the Government's rights to the C-I-P patent application (Exhibit 4b). The reviewers reiterated their assumption that the University would seek widespread commercialization in a manner that would not be anti-competitive. In the second paragraph of the "Statement of Considerations", the invention is described as a chromosome-specific staining reagent being substantially free of repetitive nucleic acid sequences. Among the various reasons for granting the waiver is: "The subject invention is complete for patent and licensing purposes".

Effective November 23, 1987 the DOE waived its rights and assigned to the University both Gray/ Pinkel patent applications. (Exhibit 5 a,b). However in so doing, the agency expressly reserved the right to require nonexclusive licensing on commercially reasonable terms upon a showing that the assignment "has tended substantially to lessen competition or result in undue market concentration" or if the invention is being underutilized.[7] Moreover the Assignment and Confirmatory License provided that any

[7]Paragraph 6, Assignment & Confirmatory License

waiver of rights may be terminated by the DOE if the request is found to contain "false material statements or nondisclosure of material facts, and such were specifically relied upon in reaching the waiver determination."[8]

In August, 1989 the University exclusively licensed the Gray and Pinkel inventions to Amoco Technology Company. The license included a right to grant sub-licenses. As a condition for the exclusive license Amoco agreed to sponsor research at LLNL. The University reserved the right to convert the license to nonexclusive if the licensee is unable to fill market demand for the licensed product.

On September 5, 1995 after nine years of prosecution at the U. S. Patent and Trademark Office, U.S. Patent No. 5,447,841 ("the '841 patent") issued. (Exhibit 6). The patent resulted from a continuation of application number 937,793 application filed in 1986. In Col. 1 of the '841 patent, lines 4-9, the following notice appears:

> The United States Government has rights in this invention pursuant to Contract No. W-7405-ENG-48 between the U. S. Department of Energy and the University of California for the Operation of Lawrence Livermore National Laboratory.

The patent covers use of "blocking DNA" in ISH which, as described in more detail in Exhibit 1(c), is needed to prevent the probe from hybridizing to repetitive sequences found in human DNA.

The day the patent issued the University of California and Vysis, a subsidiary of Amoco established to exploit the ISH intellectual property, filed suit in the Northern District of California against Oncor, Inc., a small company based in Maryland that had pioneered the commercial development of FISH probes since 1986. At the end of that year Oncor became the first company ever to receive FDA approval to market an ISH-based diagnostic. The product, a FISH gene amplification detection kit for predicting likelihood of recurrence in breast cancer, had cost Oncor over $10 million in R&D and clinical studies.

Despite this important milestone, in February of 1998 Oncor's outside auditors

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[8]Paragraph 7, Assignment & Confirmatory License

publicly expressed doubts that the company could remain a going concern in light of its negative cash flow situation. This caused a sharp decline in the company's stock price and created a crisis of confidence among investors, lenders, customers, and creditors. Faced with the mounting costs of litigation and negative publicity associated therewith, as well as the risk of a possible injunction against further sales of its lead product, made real by an unfavorable summary judgement ruling, Oncor was desperate to settle the lawsuit.

On April 9, 1998 a settlement agreement was entered. Taking advantage of Oncor's dire circumstances, the University and Amoco (now Vysis) made demands totally without precedent for a nonexclusive license to government funded technology. While the agreement remains confidential, many key terms have been published.[9] This included payments in excess of $2 million and the forced conveyance to Vysis of Oncor's entire FISH business, except for oncology products, representing more than a third of Oncor's assets at the time. The royalty rate was also exorbitant, more than double the rate Amoco/Vysis was required to pay for an exclusive license to the same intellectual property. Vysis promptly discontinued many of the genetic testing products conveyed, especially those that competed with their own, leaving a void in the market for many products.

C. Ventana Medical Systems, Inc.

Ventana Medical Systems, Inc., the Petitioner herein, develops, manufactures and markets instrument/reagent systems that automate tissue preparation and slide staining in medical laboratories worldwide. Headquartered in Tucson, Arizona, the company has pioneered the development of machines that perform immunohistochemistry (IHC), chemical stains, and ISH tests for the analysis of cells and tissues on microscope slides that were traditionally done manually. Even with fewer than 400 employees, Ventana is the worldwide leader in the automated IHC testing market, with a worldwide installed base is several times as large as the combined installed base of all of the company's current competitors.

In November of last year Ventana acquired all of Oncor's ISH business as part of an

[9] *See, e.g. Genetic Engineering News*, June 15, 1998 (Exhibit 9)

asset purchase agreement to further Ventana's expansion into DNA based testing. The University and Vysis have taken the position that the non-exclusive license in the Oncor Settlement Agreement is not transferable to Ventana, a position which Ventana disputes. Ventana met with Vysis and the University several months ago in an attempt to obtain a new license based on commercially reasonable terms. To date that effort has been unsuccessful.

II. GROUNDS FOR PETITION

A. The Exclusive License Has Resulted in Undue Market Concentration and Substantially Lessened Competition in the Line of Commerce to Which the Technology Relates.

The transfer of government rights to the University has resulted in a lessening of competition and undue market concentration among makers of gene-based diagnostics. In such cases ¶6(d)(i) of the Assignment and Confirmatory License authorizes the Secretary to require the granting of a license to Petitioner "upon terms reasonable under the circumstances."[10]

In 1989 the University exclusively licensed the subject inventions to Amoco which established the Vysis diagnostic subsidiary. The agreement gave Amoco the right to grant sublicenses. Nevertheless, it is believed that Oncor is the only manufacturer that has received a sublicense from Amoco and did so as a settlement of a lawsuit. To obtain this sublicense Amoco required Oncor not only to pay exorbitant royalties and fees but also to transfer to them whole categories of products Vysis believed competed with their own. This included the forced conveyance of Oncor's entire FISH business, except for oncology products. Many of these products were discontinued within days of being conveyed to Vysis. Furthermore, Oncor was forced to enter a covenant not to compete in the following fields: (a) FISH in any field except oncology, (b) testing of fetal cells in maternal circulation and (c) *in vitro* fertilization. (The covenant is binding on Oncor's successors as well.)

Amoco/Vysis made no secret of its intentions to remove competing products from the marketplace. John Bishop, president of Vysis, informed one industry publication that his company would be "discontinuing the Oncor products that overlap with their own."[11] The only reason a company would acquire products that it intends to discontinue is to lessen competition. This practice is directly contrary to federal technology transfer law and

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[10] The Assignment and Confirmatory License gives the DOE authority to consider market and anti-competitive factors and thus goes beyond the considerations for March-in rights under 35 USC 203.

[11] *Genetic Engineering News*, June 15, 1998

policy, which declares that government funded inventions are to be used to promote rather than restrict competition (35 U.S.C.§200) as well as the express assurances made by the University in its petition seeking a waiver. In particular, as set forth in the Background section above, the DOE questionnaire specifically asked "what will be the effect on competition and market concentration if the above requested waiver is granted?" The University answered that if the waiver were granted their licensing practice would be "consonant with the policy and objectives of Congress...to insure that inventions made by non profit organizations are used in a manner to promote free competition."

In order to obtain the license Oncor was required to agree not to compete in certain fields. While the Assignment and Confirmatory License does not require the anti-competitive behavior to necessarily rise to the level of an antitrust violation under the Clayton Act, the behavior here did likely rise to that level. It is well established that "where the patent licensor exacts a covenant from the licensee not to compete in the production or sale of related nonpatented goods this violates the antitrust laws and constitutes patent misuse."[12] Here, the University and Amoco forced Oncor to agree not to sell products in fields such as prenatal screening irrespective of whether such products are covered by a licensed patent. This constitutes patent misuse and is a violation of the antitrust laws.[13]

Amoco/Vysis' oppressive licensing practices were not directed solely at its competitor. Consumers of ISH probes–laboratories at hospitals including many nonprofit medical institutions--were threatened that they must either purchase probes exclusively from Vysis or pay up to 14% in royalties. (Exhibit 7).

Paragraph 6(d)(i) of the Assignment and Confirmatory License provides that, four years after assigning the inventions, the DOE may "require the granting of a nonexclusive or partially exclusive license to a responsible applicant or applicants, upon terms reasonable under the circumstances" if it is determined that the assignment "has tended substantially to

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[12] Einhorn, Patent Licensing, §7.04[1]

[13] Several months before the settlement Oncor offered to sell its non-oncology FISH business to Vysis for more than five million dollars. This in no way gave Vysis the right to take this business from Oncor, as a condition for the license and without any monetary consideration. It is noteworthy that Vysis continues to leverage the intellectual property to reduce competition. In negotiations with Ventana, Vysis has requested the conveyance of more than 90% of Ventana's probes as a condition of receiving a license.

lessen competition or result in undue market concentration…in any line of commerce to which the technology of the invention relates." Presumably, this provision was included to comply with the statute that permits the DOE to waive its rights to inventions made under contract only when the waiver furthers the objective of "fostering competition and preventing undue market concentration or the creation or maintenance of other situations inconsistent with the antitrust laws." 42 U.S.C. §5908. In view of the anti-competitive manner in which the subject license has been exploited, DOE intervention is appropriate.

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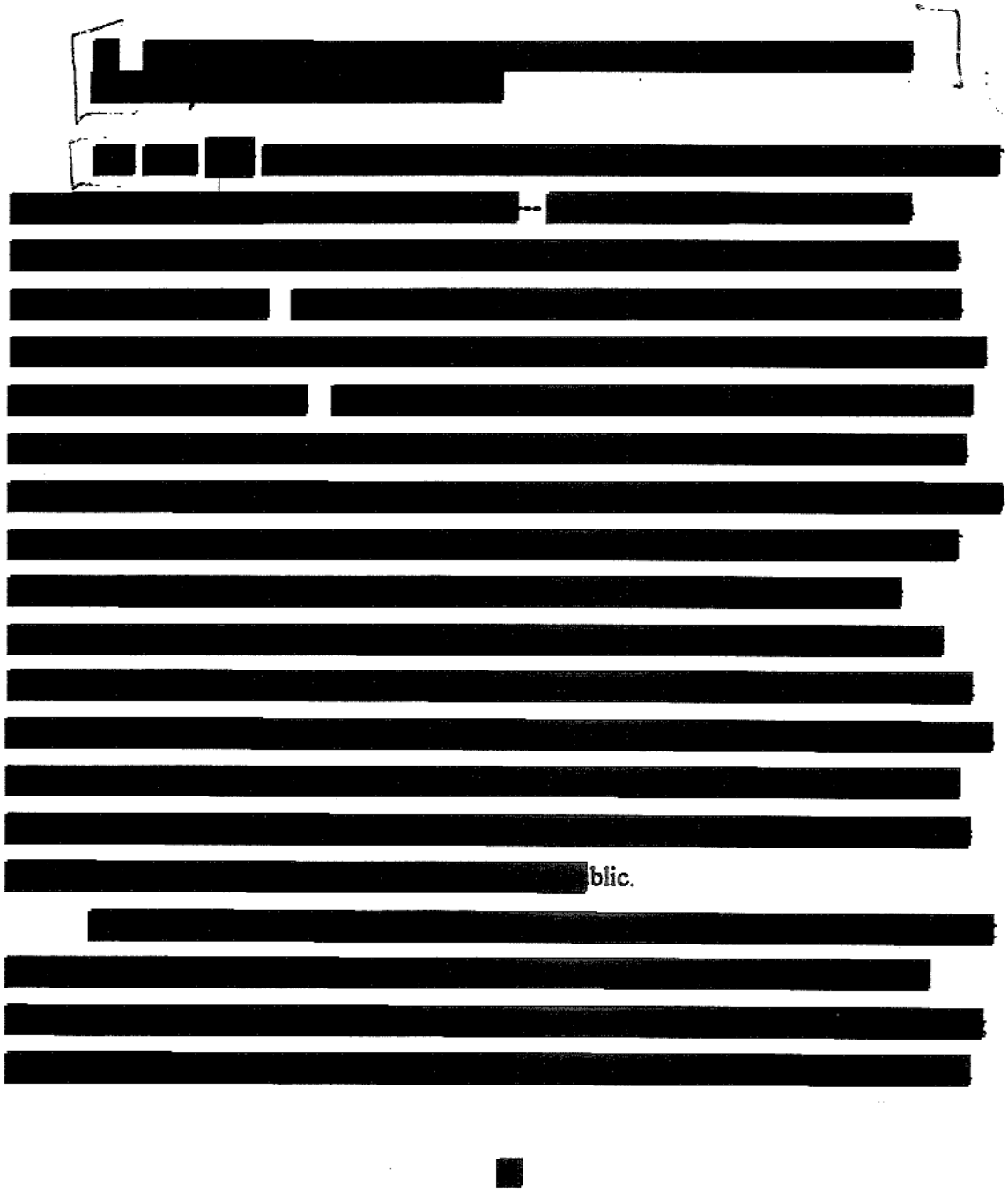

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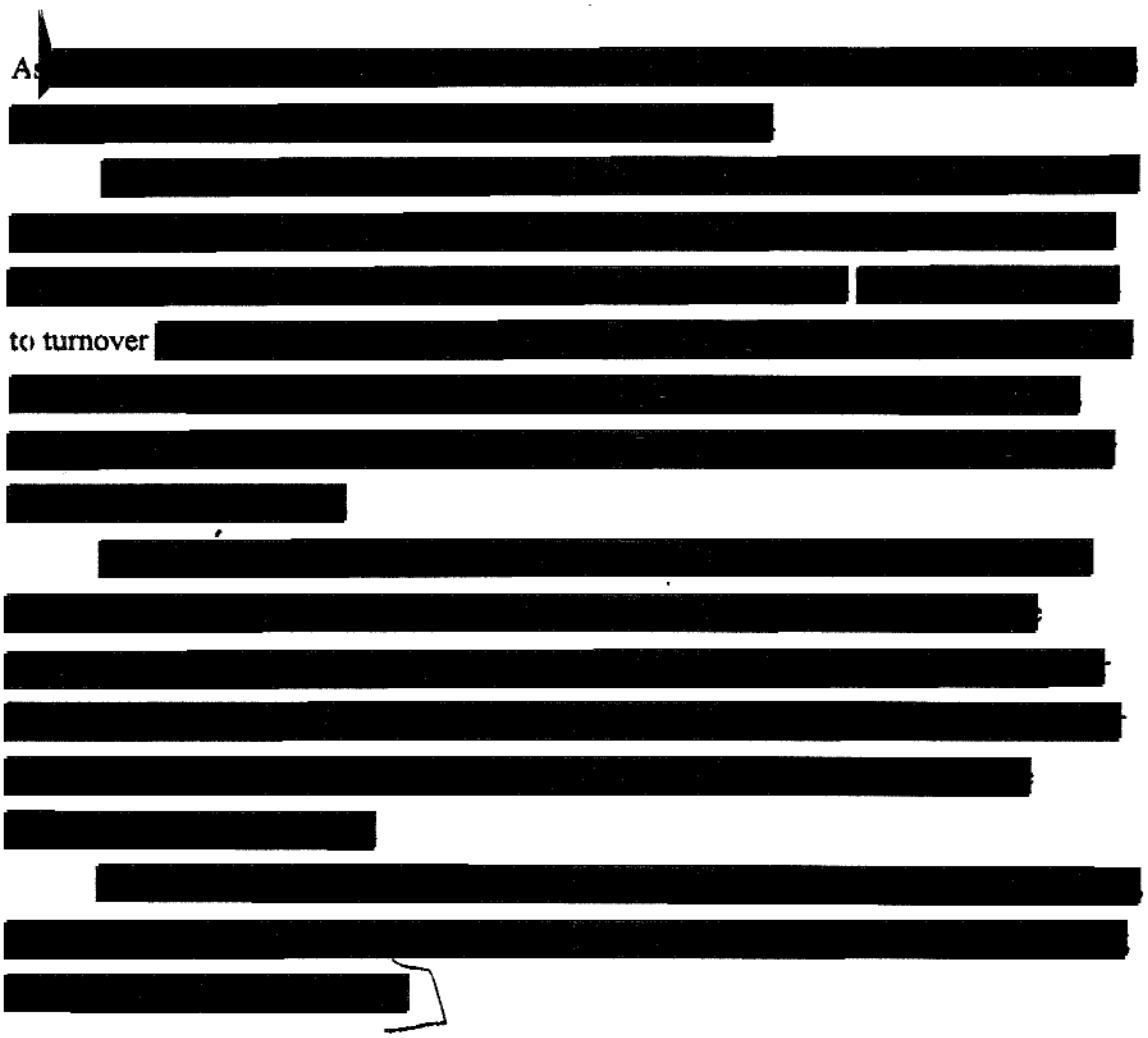

C. The DOE Relied on a Request for Waiver that Contained False Material Statements and Failed to Disclose Material Facts in Reaching the Waiver Determination

Paragraph 7 of the Assignment and Confirmatory License provides that any waiver of rights may be terminated by the DOE if the request is found to contain "false material statements or nondisclosure of material facts, and such were specifically relied upon in reaching the waiver determination." In its petitions filed on June 30, 1986 and August 14, 1986 the University (1) failed to disclose the full scope of the claimed inventions, and (2) falsely stated that it would use the intellectual property to "promote free competition", thereby giving the DOE at least two independent grounds for termination.

1. Failure to set forth full scope of claimed invention.

The prosecution history of the '841 application and the dozen applications related thereto makes clear that goal of the University from 1986 to the present has been to obtain patents covering any and all applications of ISH. Surprisingly, this goal was hidden from the DOE when they sought a waiver.

In the petitions seeking waiver the inventions were described as (i) "a method for detecting chromosomal translocations and trisomies in fetal cells", and (ii) "a method for producing single-stranded nucleic acid probes with no self-complementary sequences." (See Background, above.) This is much narrower subject matter from that claimed in the patent applications. Indeed, both applications filed in 1986 contained the following claim:

> A method of staining chromosomal DNA of a particular chromosome type or portion therof, or a particular group of chromosome types, the method comprising the steps of: providing a heterogeneous mixture of labeled nucleic acid fragments, substantial portions of each labeled nucleic acid fragment in the heterogeneous mixture having base sequences substantially complementary to base sequences of the chromosomal DNA; and,
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> reacting the heterogeneous mixture with the chromosomal DNA by in situ hybridization.

Other independent claims were directed to so-called "repeat free" probes. After twelve years of prosecution, resulting in dozens of divisions and continuing applications, the University is still seeking claims broadly covering ISH to chromosomal DNA. The descriptions in the petitions differ markedly from the subject matter of the patent applications.

Moreover, the DOE reviewers made clear that they were relying on the University's descriptions in deciding whether patent rights should be assigned stating "the invention is described in greater detail in Item 2 of the Petition for Waiver." (Exhibit 3a) Thus, the University failed to disclose material facts and offered false material statements by describing the inventions very differently from that which was in the patent application.

2. Promotion of Free Competition

In its Petitions Seeking Waiver, (Exhibit 3a,b) the University pledged that it would seek "expanded business opportunities for industrial concerns" (emphasis added) and would insure that the patent rights would be used "in a manner to promote free competition." This suggests that the University would seek to out-license the intellectual property on a nonexclusive basis. That would have been appropriate given the nature of the technology. Ely using the plural "industrial concerns" the University was suggesting that it would be seeking multiple licensees. If the University wanted an exclusive licensing arrangement this material fact should have been fully disclosed in the petitions.

In deciding whether to assign its rights to the University, the DOE gave great weight to this representation, concluding that "granting the waiver should not have an undesirable effect on competition or market concentration...Additionally, Petitioner will be a licensor with a direct interest in obtaining widespread commercialization." (Exhibit 4). In fact, however, hindsight demonstrates that the waiver has had an undesirable effect on competition for the reasons set forth in section II. A above.

In sum, we believe that the University, by virtue of the representations it made to DOE, the DOE's reliance on those representations, as well as the reservations included in the Assignments, must be willing to license the subject intellectual property to any responsible entity on commercially reasonable terms. Failure to do so entitles the entity to petition the DOE in the manner set forth in the Assignments.

D. The Contractor Has Not Given Requisite Preference to Small Business Firms in Licensing the Inventions

The modification to Contract No. W-7405-ENG-48 that was in place at the time of the of the Assignments (Modification No. M114) requires that the University give preference to small businesses in licensing the subject technology. In particular, Clause 35 (q)(2) of the contract provides as follows:

> The University agrees that it will make efforts that are reasonable under the circumstances to attract licensees

> of subject inventions that are small business firms and that it will give a preference to a small business when licensing a subject invention if the University determines that the small business firm has a plan or proposal for marketing the invention which, if executed, is equally as likely to bring the invention to practical application as any plans or proposals from applicants that are not small business firms...

On information and belief, the University has not made reasonable efforts to attract small company licensees or to provide preferential terms to such companies. To comply with this requirement the University should have insisted that Amoco, its exclusive licensee, provide small companies with nonexclusive rights at preferential rates. Instead Oncor, a small biotechnology company was provided a royalty rate more than double the rate provided a large, billion dollar oil company. Ventana has also been refused Amoco's rate.[1] Thus, the University has given preference to large businesses in licensing the inventions in clear breach of their contractual obligations to the DOE.

[1]Both Oncor and Ventana are deemed small businesses under the Small Business Investment Act of 1958, 15 U.S.C. 661 et seq. and regulations of the Small Business Administration as they both have fewer than 500 employees

III. RELIEF SOUGHT—LICENSE AGREEMENT WITH COMMERCIALLY REASONABLE TERMS

Petitioner seeks a nonexclusive world-wide license with respect to the government funded inventions of Gray and Pinkel. For the reasons which follow, Petitioner submits that reasonable licensing terms for this intellectual property would be a running royalty of four [redacted] The basis for this position is as follows.

- **Industry Standards.** According to a survey that appeared in *Genetic Engineering News,* prepared with the assistance of licensing personnel at various universities and biomedical companies, typical royalty rates for licensing *in vitro* diagnostics is between 2-6% (Exhibit 10).
- **Nonexclusivity.** The *Genetic Engineering News* study noted that the aforementioned royalty rate assumes that "licenses are exclusive worldwide since anything else diminishes the royalty rate." Where, as here, a nonexclusive license is sought, a lesser rate is appropriate.
- **Royalty Stacking.** Every sequence specific probe encounters a plethora of intellectual property encumbrances including patents to (a) specific gene sequences, (b) methods of diagnosing and assessing particular diseases or disorders, and (c) probe labeling and detection chemistries. The subject inventions relate only to particular improvements to applying probes to chromosomal DNA; they convey no rights to specific probes. A royalty of more than 4% will render ISH commercialization impractical from an economic standpoint.
- **Other License.** The royalty rates for nonexclusive sub-licenses should not exceed the rate to Amoco/Vysis for an exclusive license since the exclusive licensee earns royalty income from sub-licensees.

CONCLUSION

For the foregoing reasons it is respectfully urged that the Secretary require the granting of a nonexclusive license to the subject inventions to Petitioner upon terms reasonable under the circumstances, following a hearing upon notice thereof to the public, or, alternatively, to terminate the waiver of government rights to the subject inventions.

Respectfully Submitted,

Date: June 22, 1999

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TABLE OF EXHIBITS

Exhibit 1(a)	Overview of ISH Technique
Exhibit 1(b)	History of ISH Development
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Exhibit 2	Originally Filed Claims, in U. S. Patent Application Serial No. 819,314 filed Jan. 16, 1986
Exhibit 3(a)	University of California's First Petition For Waiver of Domestic Rights to Invention June 30, 1986
Exhibit 3(b)	University of California's Second Petition For waiver of Domestic Rights to an Identified Invention August 14, 1986
Exhibit 4(a)	Statement of Considerations to University of California's First Petition
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Exhibit 5(a)	DOE's First Assignment and Confirmatory License
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Exhibit 6	U. S. Patent No. 5,447,841 to Gray, et al.
Exhibit 7	Terms for Use Sublicenses Under the Gray, et al. U. S. Patent No. 5,447,841 for Laboratory Uses
Exhibit 8	Vysis Press Release August 17, 1999
Exhibit 9	Genetic Engineering News - Settlement Article
Exhibit 10	Genetic Engineering News - Royalty Rates