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B. Webb
8/31/99
(NE)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

AUG 06 1999

Applicants: Stavrianopoulos et al.)	
Serial No. 08/486,070)	New Group Art Unit: 1634
Filed: June 7, 1995)	Examiner: Ardin H. Marschel, Ph.D.
Title: COMPOSITION EMPLOYING CHEMIC-) ALLY LABELED OLIGONUCLEOTIDE OR POLY-) NUCLEOTIDE, AND APPARATUS AND ARRAYS) CONTAINING A COLLECTION OR SET OF SAME))	

527 Madison Avenue, 9th Floor
New York, New York 10022
July 30, 1999

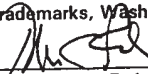
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Honorable Commissioner of Patents and Trademarks
The United States Patent and Trademark Office
Washington, D. C. 20231

COMMUNICATION
(FOLLOWING APPLICANTS' MAY 18, 1998
THIRD SUPPLEMENTAL AMENDMENT)

Dear Sir:

This is a Communication following Applicants' May 18, 1999 Third Supplemental Amendment that was filed in the above-identified application. No extension or additional fee is believed due in connection with this Communication, a Request For An Extension Of Time (3 Months) and authorization for the fee having been previously paid with Applicants' July 21, 1998 Amendment. Accordingly, this Communication is being timely filed.

EXPRESS MAIL CERTIFICATE	
"Express Mail" Label No. <u>EL369155362US</u>	
Deposit Date <u>July 30, 1999</u>	
I hereby certify that this paper and the attachments herein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington DC 20231.	
 Ronald C. Fedus Reg. No. 32,567	<u>JULY 30 99</u> Date

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REMARKS

Claims 183-376 were previously presented in Applicants' May 18, 1999 Third Supplemental Amendment. These claims continue to be presented for further examination in this application, no changes having been requested in this Communication.

The purpose of this Communication is to present evidence bearing on the commercial success of products manufactured and distributed by Enzo Diagnostics, Inc., the instant assignee of this application. Marketed under Enzo's tradenames, Enzo Bioarray™ High Yield™ RNA Transcript Labeling Kit and BioArray™ Terminal Labeling Kit, these products are being distributed by a major array or gene chip company, Affymetrix, Inc. of Santa Clara, California, for use in connection with Affymetrix GeneChip® arrays. Attached to this Communication as Exhibit A are product specification sheets for the two foregoing products. Further attached as Exhibit B are product literature sheets for Enzo's aforementioned Bioarray™ High Yield™ RNA Transcript Labeling Kit distributed by Affymetrix, Inc. in connection with its gene chips. A May 27, 1998 news release announcing the distributorship agreement between Enzo and Affymetrix in which the former will be the sole supplier of nucleic acid labeling and detection products for Affymetrix' GeneChip® arrays worldwide is also attached as Exhibit C.

The instant Assignee is also the exclusive supplier of reagent products for labeling and detecting gene sequences in connection with Flow-thru Chip™ probe arrays manufactured and sold by Gene-Logic, Inc. of Gaithersburg, Maryland. A copy of a March 23, 1999 news release announcing Enzo's arrangement with Gene-Logic is attached as Exhibit D.

Consideration to the information and documents being submitted herewith in the form of Exhibits A-D is respectfully requested.

* * * * *

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SUMMARY AND CONCLUSIONS

Claims 183-376 continue to be presented for further examination.

No other fee is believed due in connection with this Communication, a three month extension fee having been previously authorized in connection with Applicants' July 21, 1998 Amendment Under 37 C.F.R. §1.115. In the event that any other fee or fees are due, however, either in connection with this Communication or with any of Applicants' previous filings, The Patent and Trademark Office is hereby authorized to charge the amount of any other such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If it would be helpful to expediting the prosecution of this application, the undersigned may be contacted by telephone at 212-583-0100 during the daytime business hours.

Early and favorable action on this application is respectfully sought.

Respectfully submitted

A handwritten signature in black ink, appearing to read "Ronald C. Fedus".

Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

ENZO DIAGNOSTICS, INC.
c/o Enzo Biochem, Inc.
527 Madison Avenue (9th Floor)
New York, New York 10022
Telephone: (212) 583-0100
Facsimile: (212) 583-0150



**BioArray™
HighYield™
RNA Transcript Labeling Ki**

10 labeling reactions

Distributed by Affymetrix, Inc.

Part No. 900182

For Research Use Only

INTRODUCTION

The ENZO **BioArray™ HighYield™ RNA Transcript Labeling Kit** has been developed for the production of large amounts of hybridizable biotin-labeled RNA targets by *in vitro* transcription from bacteriophage T7 RNA polymerase promoters. Using T7 RNA polymerase and biotin-labeled nucleotides, large amounts of single stranded nonradioactive RNA molecules can be produced *in vitro*. Because of the nature of transcription reactions, many RNA copies of the template DNA are produced during a short incubation. Because RNA-DNA hybrids have a higher melting temperature than corresponding DNA-DNA hybrids, single-stranded RNA targets offer higher target avidity and greater sensitivity than DNA probes. RNA targets offer selectivity unavailable with DNA targets—being single stranded, they are strand-specific and hybridize more effectively to probes because the target population does not self-hybridize.

RNA transcripts that are labeled with biotin-modified ribonucleotides are used effectively in microchip array assays. The biotin-labeled RNA targets that are hybridized to arrays of DNA probes can be detected by a reporter molecule linked to streptavidin, avidin or anti-biotin antibody. Such a complex can be detected directly, *e.g.*, by excitation of a fluorophore conjugated to streptavidin, or indirectly, *e.g.*, using an enzyme conjugate that can produce an insoluble colored precipitate.

The ENZO **BioArray™ HighYield™ RNA Transcript Labeling Kit** has been formulated and optimized for use with Affymetrix GeneChip® assays. The kit contains all of the reagents required to perform 10 reactions with approximately 1 µg of transcribable cDNA template such as the product of the Affymetrix Expression Analysis Technical Manual sample preparation protocols, or a control such as plasmid template DNA (0.4 pmol).

REAGENTS PROVIDED

10X HY Reaction Buffer, 40 µl

10X DTT, 40 µl

10X Biotin Labeled Ribonucleotides, 40 µl
ATP, GTP, CTP, UTP with Bio-UTP and Bio-CTP

20X T7 RNA Polymerase, 20 µl
in Storage Buffer

10X RNase Inhibitor Mix, 40 µl
in Storage Buffer with enhancer

EQUIPMENT AND REAGENTS REQUIRED BUT NO PROVIDED

Preparation of RNA Transcripts

- Water bath or heat block set to 37°C
- DEPC-treated, sterile, deionized water

STORAGE

Store all reagents at -20°C, in a freezer that is not self-defrosting.

RNA LABELING

When preparing RNA for use with **Affymetrix GeneChip Expression Arrays**, please refer to the *Affymetrix Expression Analysis Technical Manual*, Chapter 3, "Synthesis of Biotin-Labeled cRNA (IVT)" and Chapter 4, "Control cRNA Preparation".

A. Template Preparation

For control plasmid templates, linearize the plasmid DNA using appropriate restriction enzyme digestion of the template.

- Linearized template DNA should be purified before adding to the reaction.
- Restriction enzymes that leave a 3' overhang should be avoided because T7 RNA polymerase may transcribe these in a promoter independent manner.
- Use only RNase-free water, buffers and pipette tips.

B. RNA Transcript Labeling Reaction

1. Add reaction components to RNase-free microfuge tubes.
2. Make additions in the order indicated in the following table.

NOTE: Keep reactions at room temperature while additions are made to avoid precipitation of DTT.

Reagent	Volume
Template DNA	variable to give 1 µg of cDNA or 0.4 pmol (about 1 µg of a 3.8 kb plasmid)
Distilled or deionized water	variable (to give a final reaction volume of 40 µl)
10X HY Reaction Buffer	4 µl
10X Biotin Labeled Ribonucleotides	4 µl
10X DTT	4 µl
10X RNase Inhibitor Mix	4 µl
20X T7 RNA Polymerase	2 µl
Total Volume	40 µl

3. Carefully mix the reagents and collect the mixture in the bottom of the tube by brief (5 second) microcentrifugation.
4. Immediately place the tube in a 37°C water bath. Incubate for 4 to 5 hours, gently mixing the contents of the tube every 30-45 minutes during the incubation. Longer reaction may increase yield, but the possibility of degradation by RNase increases.
5. Approximately 50-100 µg of RNA product are usually produced in each standard reaction (40 µl reaction containing 1 µg of template DNA). Larger amounts of products can be produced by scaling up all components and volumes. In most scale-up syntheses, the amount of DNA template can be reduced to 0.5-0.8 µg per 40 µl of reaction mixture.
6. Store at -20°C if not purifying RNA immediately.

PURIFICATION OF LABELED RNA TRANSCRIPTS

We recommend RNeasy spin columns from QIAGEN for purification of labeled RNA.

For Research Use Only

This product is manufactured by ENZO DIAGNOSTICS, INC. for distribution by Affymetrix, Inc. for research purposes only by the end-user and is not intended for diagnostic or therapeutic use. Purchase does not include a license or the right to utilize this product except for research purposes. Purchase does not include the right to distribute or sell this product commercially. As distributed by Affymetrix, Inc., this product may be used only in conjunction with and is permitted for use only with Affymetrix probe arrays.

For Technical Assistance call ENZO:

Toll free from the U.S. and Canada: 1-800-221-7705

All others: 516-694-7070

Fax: 516-694-7501

Affymetrix, Inc.
3380 Central Expressway
Santa Clara, CA 95051

Enzo is a registered trademark of Enzo Biochem, Inc. and BioArray is a trademark of Enzo Biochem, Inc.
Affymetrix and GeneChip are registered trademarks of Affymetrix, Inc.

This product or the use of this product is covered by one or more claims of Enzo patents including, but not limited to, the following: U.S. Patent Nos. 5,328,824 5,449,767; 5,476,928; 4,711,955 and 4,994,373; EP 0 063 879 B1; EP 0 329 198 B1 DK 171 822 B; Canadian Patent Nos. 1,219,824 and 1,309,672; Japanese Patent Nos. 2,131,226; 1,416,584 and other patents pending.

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