As filed with the Securities and Exchange Commission on September 27, 1996

SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM S-3
REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

OXiGENE, INC.
(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of incorporation or organization)

13-3679168
(I.R.S. Employer Identification No.)

110 East 59th Street, New York, NY 10022, (212) 421-0001
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

M. Andica Kunst, Esq., 110 East 59th Street, New York, NY 10022, (212) 421-0001
(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

GERALD A. EPPNER, ESQ.
BATTLE FOWLER LLP
Park Avenue Tower
75 East 55th Street
New York, New York 10022
(212) 856-7000

PETER BAARNHEILM, ADV.
DANOWSKY & PARTNERS ADVEKATBYRA
Hovslagargatan 5
S-103 22 Stockholm
Sweden
46-8 614 6400

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. / /

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. / X /

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. / /

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.
/ /

If delivery of the prospectus is expected to be made pursuant to Rule 434, please check the following box. / /

CALCULATION OF REGISTRATION FEE

Title Of Each Class Of Securities To Be Registered	Amount To Be Registered(1)	Proposed Maximum Offering Price Per Share(2)	Proposed Maximum Aggregate Offering Price(2)	Amount Of Registration Fee
Common Stock, $.01 par value	1,150,000	23.31	26,806,500.00	$9,244.00

(1) Includes 150,000 shares of Common Stock which the Underwriters have the option to purchase to cover over-allotments, if any.

(2) Pursuant to Rule 457(c), the registration fee is calculated on the basis of the average of the closing bid and asked price of the Registrant's Common Stock as reported by Nasdaq on September 23, 1996.

400608.6

OXiGENE, INC.

CROSS REFERENCE SHEET
Pursuant to Item 501(b) of Regulation S-K
Between Items Required in Part 1 of Registration Statement
(Form S-3) and Information in Prospectus

Item No.	Form S-3 Caption	Prospectus Page or Caption
1.	Forepart of Registration Statement and Outside Front Cover Page of Prospectus	Facing Page of Registration Statement; Outside Front Cover Page of Prospectus
2.	Inside Front and Outside Back Cover Pages of Prospectus	Inside Front and Outside Back Cover Pages of Prospectus
3.	Summary Information, Risk Factors and Ratio of Earnings to Fixed Charges	The Company; Prospectus Summary; Risk Factors; Management's Discussion and Analysis of Financial Condition and Results of Operations; Selected Financial Data
4.	Use of Proceeds	Use of Proceeds
5.	Determination of Offering Price	Underwriting
6.	Dilution	N/A
7.	Selling Security Holders	N/A
8.	Plan of Distribution	Outside Front Cover Page of Prospectus; Underwriting
9.	Description of Securities to be Registered	Description of Capital Stock
10.	Interests of Named Experts and Counsel	Legal Matters; Experts
11.	Material Changes	N/A
12.	Incorporation of Certain Information by Reference	Incorporation by Reference
13.	Disclosure of Commission Position on Indemnification for Securities Act Liabilities	N/A

Information contained herein is subject to completion or amendment. A registration statement relating to these securities has been filed with the Securities and Exchange Commission. These securities may not be sold nor may offers to buy be accepted prior to the time the registration statement becomes effective. This prospectus shall not constitute an offer to sell or the solicitation of an offer to buy nor shall there be any sale of these securities in any State in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities law of any such state.

PROSPECTUS (Subject to Completion)
Dated September 27, 1996

1,000,000 Shares
Common Stock
($.01 par value)

OXiGENE, INC.

The 1,000,000 shares of Common Stock ("Shares") of OXiGENE, Inc. ("Company") that are the subject of this Prospectus are being offered by the Company solely for sale to persons outside the United States in connection with a public offering of Swedish Depositary Shares ("SDSs") which is being made concurrently herewith through the underwriters named below, for whom D. Carnegie AB is acting as the Representative. When sold hereunder, the Shares will be placed in the custody of _____ ("Custodian") pursuant to a Custody Agreement, and SDSs may thereafter be traded outside the United States. At any time or from time to time following completion of this Offering, some of or all the Shares may, upon exchange of SDSs for such Shares in accordance with the terms of the Custody Agreement, be sold within and outside the United States. The Company's Common Stock is traded on the Nasdaq SmallCap Market under the symbol "OXGN." On September 23, 1996, the closing bid price of the Common Stock on that market was $23.00 per share. The Company expects that the Common Stock will be listed for trading on the Nasdaq National Market System and the SDSs will be listed for trading on the Stockholm Stock Exchange immediately following the closing of this Offering.

See "Risk Factors" Commencing on Page 9 For A Discussion of Certain Factors That Should Be Considered By Prospective Investors.

THESE SECURITIES HAVE NOT BEEN APPROVED OR DISAPPROVED BY THE SECURITIES AND EXCHANGE COMMISSION OR ANY STATE SECURITIES COMMISSION NOR HAS THE SECURITIES AND EXCHANGE COMMISSION OR ANY STATE SECURITIES COMMISSION PASSED UPON THE ACCURACY OR ADEQUACY OF THIS PROSPECTUS. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

	Price to Public	Underwriting Discounts and Commissions(1)	Proceeds to the Company(2)
Per Share (Per SDS)	$	$	$
Total(3)	$	$	$

(1) The Company has agreed to indemnify the Underwriters against certain civil liabilities under the Securities Act of 1933, as amended. See "Underwriting."
(2) Before deducting offering expenses estimated to be $250,000.00, payable by the Company.
(3) The Company has granted to the Underwriters a 30-day option to purchase up to 150,000 additional shares of Common Stock solely to cover over-allotments, if any, on the same terms and conditions as the Shares offered hereby. If such option is exercised in full, the total Price to Public, Underwriting Discounts and Commissions and Proceeds to Company will be $_____, $_____ and $_____, respectively. See "Underwriting."

The Shares (and the related SDSs) are offered by the several Underwriters, as specified herein (and in the wrap-around prospectus relating to the SDSs to which this Prospectus is attached), subject to receipt and acceptance by them and subject to their right to reject any order in whole or in part. It is expected that the Shares (and the related SDSs) will be ready for delivery in book-entry form on or about _____, 1996.

D. CARNEGIE AB

NORDBERG CAPITAL INC.

400608.6

AVAILABLE INFORMATION

The Company is subject to the informational requirements of the U.S. Securities Exchange Act of 1934 (the "Exchange Act"), and in accordance therewith files reports, proxy and information statements and other information with the United States Securities and Exchange Commission (the "SEC"). Copies of such reports, proxy and information statements and other information can be inspected and copied at the public reference facilities maintained by the SEC at Judiciary Plaza, 450 Fifth Street, N.W., Washington, D.C. 20549 and at the following Regional Offices of the SEC: Northwestern Atrium Center, 500 West Madison Street, Suite 1400, 14th Floor, Chicago, Illinois 60661; and Seven World Trade Center, 13th Floor, New York, New York 10048. Copies of such material can be obtained at prescribed rates from the Public Reference Section of the SEC, 450 Fifth Street, N.W., Washington, D.C. 20549. The SEC maintains a Web site that contains reports, proxy and information statements and other information regarding registrants that file electronically with the SEC, including the Company, and the address is (http://www.sec.gov).

The Company has filed with the SEC a registration statement on Form S-3 (together with any amendments thereto, the "Registration Statement") under the Securities Act of 1933 (the "Securities Act"), with respect to the Shares being offered pursuant to this Prospectus. This Prospectus is part of the Registration Statement and does not contain all the information set forth in the Registration Statement, certain portions of which have been omitted pursuant to the rules and regulations of the SEC. Such additional information may be obtained from the SEC's principal office in Washington, D.C. Statements contained in this Prospectus as to the contents of any contract or other document referred to herein are not necessarily complete, and in each instance reference is made to the copy of such contract or other document filed or incorporated by reference as an exhibit to the Registration Statement or incorporated by reference therein, each such statement being qualified in all respects by such reference.

INCORPORATION BY REFERENCE

This Prospectus incorporates by reference certain documents that are not presented herein or delivered herewith. These documents are available upon request from M. Andica Kunst, Esq., Vice President and Corporate Secretary, OXiGENE, Inc., 110 East 59th Street, New York, New York 10022, telephone (212) 421-0001, fax (212) 421-0475.

The Company hereby undertakes to provide without charge to each person to whom a copy of this Prospectus has been delivered, upon the written or oral request of any such person, a copy of any and all of the documents referred to which have been or may be incorporated herein by reference, other than exhibits to such documents, unless such exhibits are specifically incorporated herein by reference. Requests for such documents should be directed to the person indicated in the immediately preceding paragraph.

The following documents, which have been filed with the SEC pursuant to the Exchange Act, are hereby incorporated by reference herein:

(a) OXiGENE's Annual Report on Form 10-K, as amended, for the year ended December 31, 1995;

(b) OXiGENE's Quarterly Report on Form 10-Q for the quarter ended March 31, 1996;

(c) OXiGENE's Quarterly Report on Form 10-Q for the quarter ended June 30, 1996; and

(d) The description of the Common Stock contained in OXiGENE's Registration Statement under the Exchange Act on Form 8-A, as declared effective August 25, 1993.

All documents filed by OXiGENE pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date hereof shall be deemed to be incorporated herein by reference and to be a part hereof from the date of filing of such documents. All information appearing in this Prospectus or in any document incorporated herein by reference is not necessarily complete and is qualified in its entirety by the information and financial statements (including notes thereto) appearing in the documents incorporated by reference herein and should be read together with such information and documents.

Any statement contained in a document incorporated or deemed to be incorporated herein by reference shall be deemed to be modified or superseded for purposes of this Prospectus to the extent that a statement contained herein or in any other subsequently filed document that is deemed to be incorporated herein by reference modifies or supersedes such statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this Prospectus.

Information set forth on the cover page and under the captions "Use of Proceeds" and "Underwriting" are set forth in U.S. dollars, based on the exchange rate of $1.00 to Swedish Krone ("SEK") .1508 as published by the Wall Street Journal on Thursday, September 19, 1996.

EXCEPT FOR HISTORICAL INFORMATION CONTAINED HEREIN, THIS REGISTRATION STATEMENT CONTAINS FORWARD-LOOKING STATEMENTS WITHIN THE MEANING OF THE U.S. PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995. THESE STATEMENTS INVOLVE KNOWN AND UNKNOWN RISKS AND UNCERTAINTIES THAT MAY CAUSE THE COMPANY'S ACTUAL RESULTS OR OUTCOMES TO BE MATERIALLY DIFFERENT FROM THOSE ANTICIPATED AND DISCUSSED HEREIN. FURTHER, THE COMPANY OPERATES IN AN INDUSTRY SECTOR WHERE SECURITIES VALUES MAY BE VOLATILE AND MAY BE INFLUENCED BY REGULATORY AND OTHER FACTORS BEYOND THE COMPANY'S CONTROL. IMPORTANT FACTORS THAT THE COMPANY BELIEVES MIGHT CAUSE SUCH DIFFERENCES ARE DISCUSSED IN THE CAUTIONARY STATEMENTS ACCOMPANYING THE FORWARD-LOOKING STATEMENTS AND IN THE RISK FACTORS CONTAINED IN THIS PROSPECTUS AND IN THE RISK FACTORS DETAILED IN THE COMPANY'S OTHER FILINGS WITH THE SEC DURING THE PAST 12 MONTHS. IN ASSESSING FORWARD-LOOKING STATEMENTS CONTAINED HEREIN, READERS ARE URGED TO READ CAREFULLY ALL RISK FACTORS AND CAUTIONARY STATEMENTS CONTAINED IN THIS PROSPECTUS AND IN THOSE OTHER FILINGS WITH THE SEC.

IN CONNECTION WITH THIS OFFERING, THE UNDERWRITERS MAY OVER-ALLOT OR EFFECT TRANSACTIONS WHICH STABILIZE OR MAINTAIN THE MARKET PRICE OF THE COMMON STOCK AT A LEVEL ABOVE THAT WHICH MIGHT OTHERWISE PREVAIL IN THE OPEN MARKET. SUCH TRANSACTIONS MAY BE EFFECTED ON THE NASDAQ NATIONAL MARKET, IN THE OVER-THE-COUNTER MARKET OR OTHERWISE. SUCH STABILIZING, IF COMMENCED, MAY BE DISCONTINUED AT ANY TIME.

THE COMPANY

OXiGENE, Inc. ("OXiGENE" or the "Company") is engaged in the research and development of products designed to enhance the clinical efficacy of radiation and chemotherapy, the most common and traditional forms of non-surgical cancer treatment. The Company's proprietary technology involves the inhibition, measurement and stimulation of the cellular DNA repair process. When administered in accordance with their prescribed regimens, the Company's principal products, Sensamide(TM) and Neu-Sensamide(TM), make cancerous tumor cells more sensitive to radiation by inhibiting DNA repair activity, consequently increasing tumor damage from radiation therapy in those cells. Accordingly, the Company expects that patient response to radiation will be improved and result in increased tumor shrinkage, or reduced side effects, or both.

Currently, approximately 180 patients have been recruited in a 226-patient Phase II/III clinical trial of Sensamide(TM) in combination with radiation therapy in patients with inoperable non-small cell lung cancer. An Investigational New Drug ("IND") application with respect to this trial was filed with the U.S. Food and Drug Administration ("FDA") in 1992. At the current patient recruitment rate, the Company expects to complete patient recruitment by the end of 1996, and have results of this study available in the third quarter of 1997. OXiGENE anticipates commencing a second Phase III clinical trial in patients with non-small cell lung cancer using Neu-Sensamide(TM), the Company's reduced side effect formulation of Sensamide(TM), in the fourth quarter of 1996. The combined results of the Sensamide(TM) and Neu-Sensamide(TM) studies will serve as the basis of the Company's New Drug Application ("NDA") for Neu-Sensamide(TM) as a radiation sensitizer for the treatment of patients with non-small cell lung cancer. In March 1996, the Company filed an additional protocol under its existing IND application with the FDA to commence a Phase I/II study of Neu-Sensamide(TM) in patients with glioblastomas, a highly malignant form of brain cancer. This study started in August 1996. The FDA has advised the Company that if the Company is able to demonstrate the clinical efficacy of Neu-Sensamide(TM) in conjunction with radiation therapy in two different forms of cancer under controlled study conditions, and in two or three additional forms of cancer under uncontrolled study conditions, OXiGENE will receive product approval for Neu-Sensamide(TM) as a radiation sensitizer for all cancer indications treated with radiation. The Company believes these uncontrolled studies can be accomplished relatively quickly following the completion of this Offering.

Following a successful small-scale synthesis completed in December 1994, OXiGENE has been testing Oxi-104, a new chemical compound, in its laboratories for effects and toxicity. Although classified as an N-substituted benzamide, Oxi-104, unlike Sensamide(TM) and Neu-Sensamide(TM), is not based on the N-substituted benzamide known as metoclopramide. Oxi-104 has been designed with a molecular structure that, the Company believes, will reduce side effects while maintaining the sensitizing properties of other N-substituted benzamides. The Company currently anticipates commencing a Phase I clinical test of Oxi-104 after the filing of an IND with the FDA in the second quarter of 1997. Based on preliminary results, OXiGENE believes it can demonstrate that Oxi-104 alone can induce tumor growth-inhibiting and tumor-killing effects.

The Company's goal is to develop products that enhance the efficacy of existing forms of cancer treatment, such as radiation and chemotherapy, and improve a patient's quality of life by inhibiting the DNA repair function of, and increasing DNA damage in, tumor cells that have been subjected to treatment. The Company intends to continue and expand its ongoing clinical trial program in Europe and commence research and clinical trials in the United States. The Company's policy has been to establish relationships with universities, research organizations and other institutions in the field of oncology. The

Company intends to further strengthen these relationships, rather than expand its in-house research and clinical staff. Although the Company plans to market its products directly in certain European countries, it has had preliminary discussions with unaffiliated pharmaceutical companies regarding the formation of possible strategic alliances or joint ventures for the manufacturing and marketing of its products in the United States, the Far East and elsewhere. To date, the Company has not entered into any such alliances or ventures.

The Company's proprietary technology is based on its knowledge of the processes by which certain enzymes repair damaged DNA sites, a function essential to a cell's survival. The cell's enzymes that normally repair DNA damage counter the cytotoxic (cell-killing) effects of radiation therapy and chemotherapy by repairing the tumor cell's DNA that has been damaged by either of those therapies. Specifically, the Company utilizes its knowledge of how the DNA repair enzyme Adenosine Diphosphate Ribosyl Transferase (ADPRT) functions to improve the efficacy of radiation and chemotherapy on cancerous cells only. Sensamide(TM) and Neu-Sensamide(TM), OXiGENE's principal products, are derived from metoclopramide, a compound used for more than 30 years for other clinical indications, which inhibits ADPRT-modulated DNA repair.

The Company has also developed proprietary assays (tests) that measure levels of ADPRT in blood, thereby providing an indication of DNA repair activity that the Company believes correlates to immune function and status, and has identified a mixture of compounds that it believes may be capable of stimulating DNA repair. Based on preclinical studies to date, OXiGENE is now planning the clinical development of these product areas.

There can be no assurance that the Company's technology will prove effective, that the Company will develop any commercially accepted product, that it will obtain necessary regulatory approvals, that it will be able to enter into strategic alliances or joint ventures or that the terms thereof will be favorable to the Company, or that the Company will be profitable.

The Company was incorporated in New York in 1988, and subsequently was re-incorporated in Delaware in 1992. The Company established a Swedish subsidiary, OXiGENE (Europe) AB, in December 1994. The Company's principal executive office in the United States is located at 110 East 59th Street, New York, New York 10022 (telephone number 212-421-0001; fax number: 212-421-0475), and in Sweden at Arsenalsgatan 6, S-111 47 Stockholm, Sweden (telephone: 08-678 8720; fax number: 08-678 8605) and Scheelevagen 17, S-223 70 Lund, Sweden (telephone number: 046-16 88 60; fax number: 046-16 88 66). Any references in this Prospectus to "OXiGENE" or the "Company" shall mean OXiGENE, Inc. and its wholly-owned Swedish subsidiary OXiGENE (Europe) AB.

PROSPECTUS SUMMARY

THE OFFERING

Securities offered.....	1,000,000 shares of Common Stock. See "Description of Securities."
Common Stock to be outstanding after the Offering.....	8,647,418 shares (1)
Use of proceeds.....	To finance clinical trials and research and development activities, including acquisitions of related capital equipment, and for working capital and general corporate purposes. See "Use of Proceeds."
Risk factors.....	Investment in the Shares offered hereby involves a high degree of risk. See "Risk Factors."
Nasdaq and SSE symbols (2):	
Common Stock.....	OXGN

(1) Excludes (i) 3,293,268 shares of Common Stock subject to outstanding options, warrants and stock appreciation rights, including shares of Common Stock issuable upon exercise of 1,193,241 outstanding Public Warrants (as defined under the caption "Market Data"); and (ii) 665,000 shares of Common Stock reserved for issuance under the Company's 1996 Stock Incentive Plan. See "Capitalization," "Management - Stock Incentive Plan," "Description of Securities - Public Warrants" and Notes to the Financial Statements.

(2) The Company will make application to The Nasdaq Stock Market ("Nasdaq") to have its shares of Common Stock included in the Nasdaq National Market System upon completion of this Offering. In addition, the Company has made an application to the Stockholm Stock Exchange ("SSE") to have its shares of Common Stock in the form of SDSs listed on the SSE upon completion of this Offering.

SUMMARY OF SELECTED FINANCIAL INFORMATION

OXiGENE, Inc.
(A development stage company)

	Years Ended December 31,					Six Months Ended June 30,	
	1991	1992	1993	1994	1995	1995	1996
Statement of Operations Data:							
Total revenues	$ 17,500	$ 0	$ 50,897	$ 265,440	$ 420,949	$ 82,224	$ 253,699
Total operating expenses	519,372	1,628,667	2,070,909	3,105,199	4,138,784	1,919,045	3,665,424
Net Loss	$ (501,872)	$(1,628,667)	$(2,020,012)	$(2,839,759)	$(3,717,835)	$(1,836,821)	$(3,411,725)
Net loss per common share1	$ (0.16)	$ (0.45)	$ (0.50)	$ (0.56)	$ (0.63)	$ (0.36)	$ (0.49)

	December 31,					June 30,	
	1991	1992	1993	1994	1995	1995	1996
Balance Sheet Data:							
Cash and cash equivalents	$ 416,149	$ 164,648	$ 7,516,941	$ 1,193,999	$ 10,406,605	$ 286,114	$ 10,709,914
Securities available for sale.	0	0	0	3,291,128	502,020	2,498,820	0
Working capital	218,132	29,031	7,207,265	4,447,080	10,510,024	2,643,359	10,065,731
Deficit accumulated during the development stage	(1,193,601)	(2,822,268)	(4,842,280)	(7,682,039)	11,399,874	(9,518,859)	(14,811,599)
Total stockholders' equity	218,732	29,031	7,240,866	4,479,982	10,557,174	2,708,037	10,117,169

- --------
1 See Note 1 of the Notes to the Financial Statements for information concerning the computation of net loss per common share.

RISK FACTORS

An investment in the Shares is speculative, involves a high degree of risk and should only be made by persons who can afford a loss of their entire investment. In addition to the other information included elsewhere or incorporated by reference in this Prospectus, the following risk factors should be considered carefully in evaluating an investment in the Shares. Except as otherwise expressly set forth, information in this Prospectus does not give effect to the exercise of all or any part of the Underwriters' over-allotment option.

History of Losses and Anticipated Future Financial Results; Uncertainty of Future Profitability. The Company, as a development stage enterprise, has experienced net losses every year since its inception and, as of June 30, 1996, had a deficit accumulated during the development stage of approximately $14.8 million. The Company anticipates incurring substantial additional losses over at least the next several years due to, among other factors, the need to expend substantial amounts on research and development activities and the general and administrative expenses associated with those activities. The Company has not commercially introduced any product and its products are in varying stages of development and testing. The Company's ability to attain profitability will depend upon its ability to develop products that are effective and commercially viable, to obtain regulatory approval for the manufacture and sale of its products and to license or otherwise market its products successfully. There can be no assurance that the Company will ever achieve profitability or that profitability, if achieved, can be sustained on an ongoing basis.

Early Stage of Product Development; Unproven Safety and Efficacy. OXiGENE's products are in an early stage of development. In order to achieve profitable operations on a continuing basis, the Company, alone or in collaboration with others, must successfully develop, manufacture, introduce and market its products. The time frame necessary to achieve market success for any individual product is long and uncertain. See "Business - Drug Development and Regulatory Processes." The products currently under development by the Company will require significant additional research and development and extensive preclinical and clinical testing prior to application for commercial use. There can be no assurance that clinical testing will show any of the Company's products to be safe or efficacious. Additionally, there can be no assurance that the Company will not encounter problems in clinical trials that will cause the Company to delay or suspend clinical trials. There can also be no assurance that the Company's research or product development efforts or those of its collaborative partners, if any, will be successfully completed, or that any compounds currently under development by the Company will be successfully transformed into drugs.

Need for Additional Funds; Uncertainty of Future Funding. The Company's operations to date have consumed substantial amounts of cash. Negative cash flow from the Company's operations is expected to continue and even to accelerate in the foreseeable future. The Company's capital requirements will depend on numerous factors, including: the progress of the Company's research and development programs; progress with preclinical testing and clinical trials; the time and costs required to gain regulatory approvals; the resources the Company devotes to proprietary manufacturing methods and advanced technologies; the ability of the Company to obtain licensing arrangements; the cost of filing, prosecuting and, if necessary, enforcing patent claims; the cost of commercialization activities and arrangements; and the demand for its products if and when approved. The Company will have to raise substantial additional funds to complete development of any product or bring products to market. See "Use of Proceeds." Issuance of additional equity securities by the Company, for these or other purposes, could result in dilution to then existing stockholders, including persons purchasing the Shares. There can

be no assurance that additional financing will be available on acceptable terms, if at all. If adequate funds are not available on acceptable terms, the Company may be required to delay, scale back or eliminate one or more of its drug development programs or obtain funds through arrangements with collaborative partners or others that may require the Company to relinquish rights to certain of its technologies, product candidates or products that the Company would not otherwise relinquish, which may have a material adverse effect on the Company.

Dependence on Others for Clinical Development and Manufacturing and Marketing. OXiGENE has depended, and in the future is likely to continue to depend, on others for assistance in many areas, including conducting clinical trials, the regulatory approval process, manufacturing and marketing. Funding requirements, competitive factors or prioritization of other opportunities may lead the Company to seek additional arrangements with third parties. While OXiGENE is likely to explore license and development opportunities for its technologies with other companies, there can be no assurance that the Company will be successful in establishing and maintaining any collaborative agreements or licensing arrangements; that any collaborative partner will not be pursuing alternative technologies or developing alternative compounds either on its own or in collaboration with others, targeted at the same diseases as those involved in its collaborative arrangements with the Company; that any such collaborative partners will devote resources to the Company's technologies or compounds on a basis favorable to the Company; that any such arrangements will be on terms favorable to OXiGENE; or that, if established, such future licensees will be successful in commercializing products.

Clinical Trials; Government Regulation and Health Care Reform; Managed Care. The Company's research and development activities, preclinical and clinical trials, and the manufacturing and marketing of its products and processes are subject to extensive regulation by numerous governmental authorities in the United States and other countries. Preclinical and clinical trials and manufacturing and marketing of OXiGENE's products and processes are and will continue to be subject to the rigorous testing and approval processes of the U.S. Food and Drug Administration ("FDA"), the Swedish Medical Products Agency and other corresponding foreign regulatory authorities. The regulatory process can take many years and require the expenditure of substantial resources. In addition, delays or rejections may be encountered during the period of product development and FDA regulatory review of each submitted application. Similar delays may also be encountered in foreign countries. There can be no assurance that, even after such time and expenditures, regulatory approval will be obtained for any products developed by OXiGENE or that a product, if approved in one country, will be approved in other countries. See "Business - Drug Development and Regulatory Processes." Moreover, if regulatory approval of a product is granted, such approval may entail limitations on the indicated uses for which that product may be marketed. Further, even if such regulatory approval is obtained, a marketed product, its manufacturer and its manufacturing facilities, are subject to continual review and periodic inspections, and later discovery of previously unknown problems (such as previously undiscovered side effects) with a product, manufacturer or facility may result in restrictions on such product, manufacturer or facility, including a possible withdrawal of the product from the market. Failure to comply with the applicable regulatory requirements can, among other things, result in fines, suspensions of regulatory approvals, product recalls, operating restrictions, injunctions and criminal prosecution. Additionally, further government regulation may be established which could prevent or delay regulatory approval of the Company's products. Further, the U.S. Congress continues to debate various health care reform proposals which, if adopted, may have a material adverse effect on the Company. Moreover, cost control initiatives that stem from the ongoing increase in health care maintenance programs may affect the financial ability and willingness of patients and their health care providers to utilize certain therapies.

Competition and Risk of Technological Obsolescence. The Company is engaged in a rapidly evolving field. Competition from other pharmaceutical companies, biotechnology companies and other research and academic institutions is intense and expected to increase. Many of those companies and institutions have substantially greater financial, technical and human resources than the Company. Those companies and institutions also have substantially greater experience in developing products, in obtaining regulatory approval and in manufacturing and marketing pharmaceutical products. Accordingly, competitors may succeed in obtaining regulatory approval for their products more rapidly than the Company. The Company also competes with universities and other research institutions in the development of products, technologies and processes. Competitors have developed or are in the process of developing technologies that are, or in the future may be, the basis for competitive products. Some of those products may have an entirely different approach or means of accomplishing the desired therapeutic effect than products being developed by the Company. See "Business-Competition." There can be no assurance that the Company's competitors will not succeed in developing technologies and products that are more effective than those being developed by the Company or that would render the Company's technology and products less competitive or even obsolete. In addition, one or more of the Company's competitors may achieve product commercialization or patent protection earlier than the Company, which could materially adversely affect the Company.

Dependence on Patents and Proprietary Technology. To date, OXiGENE's principal therapeutic products, Sensamide(TM) and Neu-Sensamide(TM), have been based on certain available compounds that are produced by others, and its newest compound, Oxi-104, is a synthetic compound discovered by the Company. The Company anticipates that products it develops hereafter may include or be based on the same or other compounds owned or produced by unaffiliated parties, as well as other synthetic compounds it may discover. Although the Company expects to seek patent protection for any compounds it discovers and/or for the specific use of any such compounds, there is no assurance that any or all of them will be subject to effective patent protection. Further, the development of regimens for the administration of pharmaceuticals, which generally involve specifications for the frequency, timing and amount of dosages, has been, and the Company believes may continue to be, important to the Company's efforts, although those processes, as such, may not be patentable.

The Company's success will depend, in part, on its ability to obtain patents, protect its trade secrets and operate without infringing on the proprietary rights of others. The Company has filed applications for several U.S. and international patents on its principal technologies. The patent position of pharmaceutical and biotechnology firms like OXiGENE generally is highly uncertain and involves complex legal and factual questions, resulting in both an apparent inconsistency regarding the breadth of claims allowed in U.S. patents and general uncertainty as to their legal interpretation and enforceability. Accordingly, there can be no assurance that the Company's patent applications will result in patents being issued, that any issued patents will provide the Company with competitive protection or will not be challenged by others, or that the patents of others will not have an adverse effect on the ability of the Company to do business. Moreover, since some of the basic research relating to one or more of the Company's patent applications and/or patents was performed at various universities and/or funded by grants, particularly in Sweden, there can be no assurance that one or more universities and/or grantors will not assert that they have certain rights in such research, although the Company is not aware of any such assertions or any basis therefor. Furthermore, there can be no assurance that others will not independently develop similar products, will not duplicate any of the Company's products or, if patents are issued to the Company, will not design around such patents. In addition, the Company may be required to obtain licenses to patents or other proprietary rights of others. No assurance can be given that any licenses required under any such patents or proprietary rights would be made available on terms

acceptable to the Company, if at all. If the Company does not obtain such licenses, it could encounter delays in product market introductions while it attempts to design around such patents, or could find that the development, manufacture or sale of products requiring such licenses is foreclosed. In addition, the Company could incur substantial costs in defending itself in suits brought against it or in connection with patents to which it holds a license or in bringing suit to protect the Company's own patents against infringement. Although the Company has confidentiality agreements with the institutions that perform its preclinical and clinical tests, the Company has no such agreements with the employees of such institutions, and there can be no assurance that these employees will abide by the terms of such agreements. See "Business - Patents and Trade Secrets."

Product Liability Exposure; No Insurance Coverage. The use of the Company's technology in clinical trials and sales based on it may expose the Company to liability claims. These claims could be made directly by consumers or by pharmaceutical companies or others involved in the application of the Company's technology. The Company has no liability coverage for its ongoing clinical trials, and there can be no assurance that such coverage will be available at a reasonable cost and in amounts sufficient to protect the Company against claims or recalls that could have a material adverse effect on the financial condition and prospects of the Company. Further, adverse product and similar liability claims could negatively impact the Company's ability to obtain or maintain regulatory approvals for its technology.

Price Volatility of the Shares. Securities of pharmaceutical research and development companies have experienced extreme price and volume fluctuations which have often been unrelated to operating performance. See "Market Data." Announcements of research developments by the Company or by its competitors may have a significant effect on the Company's business and on the market price of the Company's shares of Common Stock. The price and liquidity of the Shares (or the SDSs) may also be significantly affected by trading activity and market factors related to the SDS market or to the market for the Shares, as the case may be, which factors and the effects thereof may differ between those markets.

Dependence on Certain Officers and Directors. The Company believes that its success is, and will likely continue to be, materially dependent upon its ability to retain the services of certain of its current officers and directors, particularly Dr. Bjorn Nordenvall, its Chief Executive Officer, Dr. Claus Moller, its Chief Medical Officer, and Dr. Ronald Pero, its Chief Scientific Officer. The loss of the services of any of these individuals could have a material adverse effect on the Company. Additionally, the Company believes that it may, at any time and from time to time, be materially dependent on the services of consultants and other unaffiliated third parties.

MARKET DATA

On August 26, 1993, the Company completed an initial public offering of 1,605,000 units, each unit consisting of one share of the Company's common stock, par value $.01 per share ("Common Stock"), and a warrant ("Public Warrant") to purchase one additional share of Common Stock. See "Description of Securities." The Common Stock and Public Warrants are listed for quotation under the symbols "OXGN" and "OXGNW," respectively, on the Nasdaq SmallCap System. An application will be made to list the Company's Common Stock and Public Warrants on the Nasdaq National Market System, to be effective upon completion of this Offering. The following table sets forth the high and low per share and per warrant bid prices for the Common Stock and Public Warrants, respectively, for each quarterly period within the Company's two most recent fiscal years and for the first three quarters, through September 23, 1996, of 1996.

	Common Stock		Public Warrants	
Fiscal Year	High	Low	High	Low
1994				
First Quarter	$7.50	$5.75	$3.38	$2.13
Second Quarter	10.50	5.50	4.75	2.00
Third Quarter	10.25	5.50	4.75	2.00
Fourth Quarter	7.88	4.63	1.88	.88
1995				
First Quarter	$7.25	$4.63	$2.00	$1.00
Second Quarter	7.38	5.13	2.13	1.44
Third Quarter	7.75	6.38	2.63	1.75
Fourth Quarter	11.75	5.75	3.63	1.75
1996				
First Quarter	$23.13	$9.25	$15.00	$2.88
Second Quarter	32.13	17.50	23.50	10.25
Third Quarter (through September 23, 1996)	27.00	16.75	17.75	8.50

On September 23, 1996, the high and low per share and per warrant bid price for the Common Stock and Public Warrants was $24.75, and $23.00, and $14.25, and $13.00, respectively.

As of August 30, 1996, there were 55 holders of record of the Company's Common Stock and 4 holders of record of the Company's Public Warrants. The Company believes, based on the number of proxy statements and related materials distributed in connection with its 1996 Annual Meeting of Stockholders, that there are more than 1,250 beneficial owners of its Common Stock.

USE OF PROCEEDS

The net proceeds to the Company from the sale of the 1,000,000 Shares (and the related SDSs) offered hereby (at an assumed public offering price of $23.00 per Share, which was the closing bid price of the Company's Common Stock on September 23, 1996) are estimated to be $21.6 million (approximately $24.9 million if the Underwriters' over-allotment option for 150,000 shares of Common Stock is exercised in full), after deducting the underwriting discount and offering expenses payable by the Company.

The Company intends to use the net proceeds as follows: (i) approximately $16.0 million (or $18.0 million if the Underwriters' over-allotment option is exercised in full) for funding activities related to the Company's products that are currently under development, including providing funds in connection with related ongoing research and development and capital expenditures, clinical trials and regulatory applications; (ii) approximately $2.6 million (or $3.9 million if the Underwriters' over-allotment option is exercised in full) for research, development, sales and marketing costs and related capital expenditures, including equipment, in connection with additional potential products and uses for the Company's technology; and (iii) the balance, approximately $3.0 million for working capital and general corporate purposes.

The amounts and timing of actual expenditures will depend upon numerous factors, including primarily the timing of the Company's regulatory applications as well as the progress of its research and development programs and clinical trials. Additionally, it is the Company's policy regularly to review potential opportunities to acquire, or to enter into joint venture or licensing relationships with respect to, products and businesses compatible with its existing business. The Company may, therefore, use a portion of the net proceeds to make acquisitions or to fund joint research and development or other complementary ventures or strategic alliances, although the Company does not currently have any arrangements, agreements or understandings with respect thereto.

The Company believes that the net proceeds of this Offering, together with cash flow from operations, if any, and interest earned on its cash and cash equivalent balances, will be sufficient to finance its cash requirements for at least a period of approximately 24 months from the date of this Prospectus. The Company will be required to finance its business through borrowing or by raising additional equity capital until such time as (i) it can commercially exploit its technology, either through licensing arrangements or the sale of products based on its technology, and (ii) revenues from those commercial activities become sufficient to cover its expenses. As the Company expects that the capital it has on hand and the net proceeds from this Offering will not be sufficient to carry it through all that time, the Company anticipates that it will need to obtain additional financing, the amount and timing of which is currently uncertain and the availability of which, on terms reasonably acceptable to the Company, if at all, cannot be assured.

Pending the aforementioned uses, the net proceeds of this Offering will be invested in U.S. Government securities; short-term, investment grade securities; customary bank deposits maintained at first class banks in Sweden or the United States; or other short-term, interest bearing financial instruments that will not cause the Company to become an "investment company" within the meaning of the U.S. Investment Company Act of 1940.

CAPITALIZATION

The following table sets forth the capitalization of the Company at June 30, 1996, and as adjusted at that date to reflect the sale by the Company of the Shares (and related SDSs) and the receipt of the estimated net proceeds therefrom, as set forth under the caption "Use of Proceeds."

	June 30, 1996(1)	
	(All amounts in thousands)	
	Actual	As Adjusted
Stockholders' equity:		
Common Stock, $.01 par value, 15,000,000 shares authorized, 7,271,282 shares issued and outstanding; 8,271,282 issued and outstanding, as adjusted(2)(3)	$ 72	$ 82
Additional paid-in capital	24,853	46,443
Common Stock subscribed	98	--
Subscription receivable	(98)	--
Foreign currency translation adjustment	3	3
Deficit accumulated during the development stage	(14,811)	(14,811)
Total stockholders' equity	$ 10,117	$ 31,717

(1) At June 30, 1996, the Company did not have any long-term or short-term debt.

(2) At the 1996 Annual Meeting of Stockholders, the Company's stockholders approved an amendment to the Company's Amended and Restated Certificate of Incorporation, increasing the number of authorized shares of Common Stock from 15 million to 60 million shares. No amendment to the Company's Amended and Restated Certificate of Incorporation has been filed to date.

(3) Excludes (i) 3,293,268 shares of Common Stock subject to outstanding options, warrants and stock appreciation rights, including shares of Common Stock issuable upon exercise of 1,193,241 outstanding Public Warrants (as defined under the caption "Market Data"); and (ii) 665,000 shares of Common Stock reserved for issuance under the Company's 1996 Stock Incentive Plan. See "Capitalization," "Management - Stock Incentive Plan," "Description of Securities - Public Warrants" and Notes to the Financial Statements.

DIVIDEND POLICY

The Company has not paid any cash dividends since its inception and does not intend to pay any cash dividends in the foreseeable future. The Company currently intends to retain future earnings, if any, to finance the growth and development of its business.

SELECTED FINANCIAL INFORMATION

The following selected financial information for each of the five years in the period ended December 31, 1995, have been derived from the company's financial statements, which statements have been audited by Ernst & Young LLP, independent auditors, as set forth in their report included elsewhere herein. The following selected financial information for the six months ended June 30, 1995 and 1996, has been derived from unaudited financial statements which, in the opinion of management of the Company, reflect all adjustments, consisting only of normal recurring adjustments, necessary to present fairly the financial data for such periods. Operating results for the six months ended June 30, 1996 are not necessarily indicative of the results that may be expected for the year ending December 31, 1996. All of the financial information set forth below should be read in conjunction with the financial statements and notes thereto included elsewhere in this Prospectus and also with the information appearing under the caption "Management's Discussion and Analysis of Financial Condition and Results of Operations."

Summary Financial Information

OXiGENE, Inc.
(A development stage company)

	Years Ended December 31,					Six Months Ended June 30,	
	1991	1992	1993	1994	1995	1995	1996
Statement of Operations Data:							
Revenues:							
Research income	$ 17,500	$ -	$ -	$ -	$ -	$ -	$ -
Interest income	-	-	50,897	265,440	420,949	82,224	253,699
Total revenues	17,500	-	50,897	265,440	420,949	82,224	253,699
Operating Expenses:							
Research and development	284,032	910,937	879,195	1,764,462	2,843,593	1,273,221	2,356,395
General and administrative	235,340	717,730	1,191,714	1,340,737	1,295,191	645,824	1,309,029
Total operating expenses	519,372	1,628,667	2,070,909	3,105,199	4,138,784	1,919,045	3,665,424
Net Loss	$ (501,872)	$(1,628,667)	$(2,020,012)	$(2,839,759)	$(3,717,835)	$(1,836,821)	$(3,411,725)
Net loss per common share1	$ (0.16)	$ (0.45)	$ (0.50)	$ (0.56)	$ (0.63)	$ (0.36)	$ (0.49)
Weighted average number of common shares outstanding (in thousands)(1)	3,177	3,613	4,026	5,037	5,876	5,058	6,971

- --------

1 See Note 1 of the Notes to the Financial Statements for information concerning the computation of net loss per common share.

	December 31,					June 30,	
	1991	1992	1993	1994	1995	1995	1996
Balance Sheet Data:							
Cash and cash equivalents.....	$ 416,149	$ 164,648	$ 7,516,941	$ 1,193,999	$ 10,406,605	$ 286,114	$ 10,709,914
Cash and cash equivalents.....	$ 416,149	$ 164,648	$ 7,516,941	$ 1,193,999	$ 10,406,605	$ 286,114	$ 10,709,914
Securities available for sale.	0	0	0	3,291,128	502,020	2,498,820	0
Working capital.....	218,132	29,031	7,207,265	4,447,080	10,510,024	2,643,359	10,065,731
Total assets.....	417,272	192,344	7,550,836	4,770,951	11,227,251	2,946,848	10,938,767
Total liabilities.....	198,540	163,313	309,970	290,969	670,077	238,809	821,598
Deficit accumulated during the development stage.....	(1,193,601)	(2,822,268)	(4,842,280)	(7,682,039)	(11,399,874)	(9,518,859)	(14,811,599)
Total stockholders' equity....	218,732	29,031	7,240,866	4,479,982	10,557,174	2,708,037	10,117,169

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATION

Overview

OXiGENE is a development-stage pharmaceutical company engaged in the research and development of products designed to enhance the clinical efficacy of radiation and chemotherapy, the most common and traditional forms of non-surgical cancer treatment. OXiGENE has devoted substantially all of its efforts and resources to research and development conducted on its own behalf and through strategic collaborations with clinical institutions and other organizations, particularly the University of Lund in Lund, Sweden. Consequently, OXiGENE believes that its research and development expenditures have been somewhat lower than other comparable development-stage pharmaceutical companies. OXiGENE has generated a cumulative net loss of approximately $14.8 million for the period from its inception through June 30, 1996. OXiGENE expects to incur significant additional operating losses over the next several years, principally as a result of its continuing clinical trials and anticipated research and development expenditures. The major source of OXiGENE's working capital has been the proceeds of private and public equity financings. As of June 30, 1996, OXiGENE had no long-term debt or loans payable.

Results of Operations

Six Months Ended June 30, 1996 and 1995

During the six month periods ended June 30, 1996 and 1995, the Company had no revenues, except approximately $0.3 million and $0.1 million of interest income, respectively. The Company's total operating expenses for those periods were approximately $3.7 million and $1.9 million, respectively. Research and development expenses for the six month period ended June 30, 1996 increased to approximately $2.4 million from approximately $1.3 million for the comparable 1995 period. The increase in reported research and development expenses was attributable to a charge for financial reporting purposes of approximately $1.0 million. This charge was recorded because the market value per share of Common Stock on June 30, 1996 ($25.50) exceeded the exercise price of stock appreciation rights previously granted by the Company to certain clinical investigators and consultants. Without giving effect to such charge, research and development expenses increased by approximately $0.1 million compared to the comparable 1995 period. Generally, the Company makes payments to its clinical investigators if and when certain predetermined milestones in its clinical trials are reached, rather than on a fixed quarterly or monthly basis. As a result of the foregoing and the existence of outstanding stock appreciation rights, research and development expenses have fluctuated, and are expected to continue to fluctuate, from quarter to quarter. General and administrative expenses for the six month period ended June 30, 1996 increased to approximately $1.3 million from approximately $0.6 million for the comparable 1995 period. The increase in general and administrative expenses is primarily attributable to (i) investment banking fees paid to D. Carnegie AB ("Carnegie") of Stockholm, Sweden and (ii) start-up expenses related to establishing OXiGENE's subsidiary in Sweden. In an effort to preserve cash and reduce cash flow requirements, the Company's policy has been to minimize the number of employees and to use outside consultants to the extent practicable. OXiGENE expects that its clinical trial expenses will increase significantly as it proceeds with and expands the Neu-Sensamide(TM) clinical trial program and it initiates research and clinical trials on new compounds, including Oxi-104.

Three Year Period Ended December 31, 1995

Year Ended December 31, 1995 Compared to Year Ended December 31, 1994. OXiGENE had no revenues, except for approximately $0.4 million and $0.3 million of interest income in the years ended December 31, 1995 and 1994, respectively. The increase in interest income is attributable to the investment of the net proceeds received by the Company from a private placement financing completed in July 1995. Total operating expenses for the year ended December 31, 1995 increased to approximately $4.1 million from approximately $3.1 million for the comparable 1994 period. Research and development expenses for the year ended December 31, 1995 increased to approximately $2.8 million from approximately $1.8 million for the comparable 1994 period, while general and administrative expenses remained virtually unchanged. The increase in operating expenses is primarily due to (i) the costs and expenses associated with an expansion of the clinical trial program, (ii) increases in research and development activities in connection with OXiGENE's new compounds, and (iii) the expenses related to OXiGENE's subsidiary in Sweden.

Year Ended December 31, 1994 Compared to Year Ended December 31, 1993. OXiGENE had no revenues, except for interest income of approximately $0.3 million and $0.1 million in the years ended December 31, 1994 and 1993, respectively. Total operating expenses for the year ended December 31, 1994 increased to $3.1 million from $2.1 million for the comparable 1993 period, reflecting accelerated clinical activities. OXiGENE's research and development expenses for the year ended December 31, 1994, increased to approximately $1.8 million from approximately $0.9 million in the comparable 1993 period. The increase in research and development expenses was primarily due to the commencement of OXiGENE's Phase II/III clinical trials of Sensamide(TM) and additional research and development efforts. OXiGENE's general and administrative expenses for the year ended December 31, 1994, increased to approximately $1.3 million from $1.2 million in the comparable 1993 period.

Liquidity and Capital Resources

OXiGENE has experienced net losses and negative cash flow from operations each year since its inception and, as of June 30, 1996, had a deficit during the development stage of approximately $14.8 million. The Company expects to incur substantial additional expenses, resulting in significant losses, over the next several years as it continues to increase its research and development activities and expands its clinical trial program. To date, the Company has financed its operations primarily through the net proceeds it has received from private and public equity financings.

In July 1995, OXiGENE completed a $10.0 million private placement with net proceeds to the Company of approximately $9.5 million. Carnegie acted as placing agent for this transaction. The Company has used and anticipates that it will continue to use the proceeds from the private placement for current and expanded clinical trials and for research and development activities. OXiGENE had cash, cash equivalents and marketable securities of approximately $10.7 million and $10.9 million at June 30, 1996 and December 31, 1995, respectively. The relatively minor decrease in cash equivalents is due to the receipt by OXiGENE of approximately $1.7 million from the exercise of outstanding options and warrants during the six month period ended June 30, 1996, offset by net cash used in operating activities during the six months ended June 30, 1996, of $1.9 million.

OXiGENE's policy is to contain its fixed expenditures by maintaining a relatively small number of employees and relying as much as possible on outside services for its clinical research and clinical trials. A quarterly retainer is being paid to the University of Lund, Lund, Sweden, for preclinical

research. For the years ended December 31, 1995, 1994 and 1993, the amount of such retainer was approximately $0.2 million, $0.4 million and $0.1 million, respectively. The significant increase in the amount paid to the University of Lund prior to 1995, is due to the fact that clinical trial expenses were billed to the Company through the University of Lund. Since 1995, such expenses have been paid by the Company directly. Accordingly, the amount paid to the University of Lund decreased correspondingly. For the six-month period ended June 30, 1996 such amount was approximately $0.1 million. In addition, in late 1991, OXiGENE engaged Cato Research, Ltd. ("Cato") in Durham, North Carolina, to, among other things, monitor OXiGENE's clinical trials. The amount billed to OXiGENE by Cato during the years ended December 31, 1995, 1994 and 1993 was approximately $0.7 million, $0.6 million and $0.5 million, respectively. The continuous increase in the amount billed by Cato reflects the expenses associated with the acceleration of OXiGENE's Phase II/III clinical trial for Sensamide(TM) and monitoring and supporting the development of Neu-Sensamide(TM). For the six month period ended June 30, 1996, the amount paid to Cato was approximately $0.4 million. Further, in June 1996, in collaboration with ILEX(TM) Oncology Inc. ("ILEX"), a contract research organization in Austin, Texas, a large-scale synthesis of Oxi-104 in accordance with FDA current U.S. Good Laboratory Practice standards ("cGLP") was established. To date, the Company has paid ILEX approximately $0.3 million. As the research and development and clinical trials with respect to Oxi-104 continue, the Company expects that the amounts payable to ILEX from time to time will increase significantly.

OXiGENE anticipates that the net proceeds of this Offering, together with its existing cash and cash equivalents, will satisfy OXiGENE's projected cash requirements for at least the next 30 months. See "Use of Proceeds." However, working capital and capital requirements may vary materially from those now planned due to numerous factors including, but not limited to, the progress of OXiGENE's research and development programs, the results of preclinical testing and clinical trials, the timing and costs involved in obtaining regulatory approvals, the level of resources that will be devoted to the development of manufacturing, marketing and sales capabilities, technological advances, the approval of pending patent applications and the status of collaborative agreements with other companies, if any, to provide funding and services to OXiGENE to support or defray some of or all the costs associated with any of or all these activities. The Company anticipates that it will have to seek substantial additional private or public financing or enter into a collaborative arrangement with one or more third parties to complete the development of any product or bring products to market. There can be no assurance that additional financing will be available on acceptable terms, if at all.

OXiGENE has no material commitments for capital expenditures as of June 30, 1996.

BUSINESS

Introduction

OXiGENE is engaged in the research and development of products designed to enhance the clinical efficacy of radiation and chemotherapy, the most common and traditional forms of non-surgical cancer treatment. The Company's proprietary technology involves the inhibition, measurement and stimulation of the cellular DNA repair process. When administered in accordance with their prescribed regimens, the Company's principal products, Sensamide(TM) and Neu-Sensamide(TM), make cancerous tumor cells more sensitive to radiation by inhibiting DNA repair activity, consequently increasing tumor damage from radiation therapy in those cells. Accordingly, the Company expects that patient response to radiation will be improved and result in increased tumor shrinkage, or reduced side effects, or both.

Currently, approximately 180 patients have been recruited in a 226-patient Phase II/III clinical trial of Sensamide(TM) in combination with radiation therapy in patients with inoperable non-small cell lung cancer. An Investigative New Drug ("IND") application with respect to this trial was filed with the FDA in 1992. At the current patient recruitment rate, the Company expects to complete patient recruitment by the end of 1996, and have results of this study available in the third quarter of 1997. OXiGENE anticipates commencing a second Phase III clinical trial in patients with non-small cell lung cancer using Neu-Sensamide(TM), the Company's reduced side effect formulation of Sensamide(TM), in the fourth quarter of 1996. The combined results of the Sensamide(TM) and Neu-Sensamide(TM) studies will serve as the basis of the Company's New Drug Application ("NDA") for Neu-Sensamide(TM) as a radiation sensitizer for the treatment of patients with non-small cell lung cancer. In March 1996, the Company filed an additional protocol under its existing IND application with the FDA to commence a Phase I/II study of Neu-Sensamide(TM) in patients with glioblastomas, a highly malignant form of brain cancer. This study started in August 1996. The FDA has advised the Company that if the Company is able to demonstrate the clinical efficacy of Neu-Sensamide(TM) in conjunction with radiation therapy in two different forms of cancer under controlled study conditions, and in two or three additional forms of cancer under uncontrolled study conditions, OXiGENE will receive product approval for Neu-Sensamide(TM) as a radiation sensitizer for all cancer indications treated with radiation. Although the Company cannot predict the outcome, it believes the conduct of these uncontrolled studies can be accomplished relatively quickly following completion of this Offering because selection of the forms of cancer to be tested will be in the sole discretion of the Company, each study is expected to be conducted on not more than 50 patients and simultaneous control group studies will not be required, success being determined solely by comparing the studies' results with generally available historical data.

Following a successful small-scale synthesis completed in December 1994, OXiGENE has been testing Oxi-104, a new chemical compound, in its laboratories for effects and toxicity. Although classified as an N-substituted benzamide, Oxi-104, unlike Sensamide(TM) and Neu-Sensamide(TM), is not based on the N-substituted benzamide known as metoclopramide. Oxi-104 has been designed with a molecular structure that, the Company believes, will reduce side effects while maintaining the sensitizing properties of other N-substituted benzamides. The Company currently anticipates commencing a Phase I clinical test of Oxi-104 after the filing of an IND with the FDA in the second quarter of 1997. Based on preliminary results, OXiGENE believes it can demonstrate that Oxi-104 alone can induce tumor growth-inhibiting and tumor-killing effects.

The Company's goal is to develop products that enhance the efficacy of existing forms of cancer treatment, such as radiation and chemotherapy, and improve a patient's quality of life by inhibiting the DNA repair function of, and increasing DNA damage in, tumor cells that have been subjected to treatment. The Company intends to continue and expand its ongoing clinical trial program in Europe and commence research and clinical trials in the United States. The Company's policy has been to establish relationships with universities, research organizations and other institutions in the field of oncology. The Company intends to further strengthen these relationships, rather than expand its in-house research and clinical staff. Although the Company plans to market its products directly in certain European countries, it has had preliminary discussions with unaffiliated pharmaceutical companies regarding the formation of possible strategic alliances or joint ventures for the manufacturing and marketing of its products in the United States, the Far East and elsewhere. To date, the Company has not entered into any such alliances or ventures.

The Company's proprietary technology is based on its knowledge of the processes by which certain enzymes repair damaged DNA sites, a function essential to a cell's survival. The cell's enzymes that normally repair DNA damage counter the cytotoxic (cell-killing) effects of radiation therapy and chemotherapy by repairing the tumor cell's DNA that has been damaged by either of those therapies. Specifically, the Company utilizes its knowledge of how the DNA repair enzyme Adenosine Diphosphate Ribosyl Transferase (ADPRT) functions to improve the efficacy of radiation and chemotherapy on cancerous cells only. Sensamide(TM) and Neu-Sensamide(TM), OXiGENE's principal products, are derived from metoclopramide, a compound used for more than 30 years for other clinical indications, which inhibits ADPRT-modulated DNA repair.

The Company has also developed proprietary assays (tests) that measure levels of ADPRT in blood, thereby providing an indication of DNA repair activity that the Company believes correlates to immune function and status, and has identified a mixture of compounds that it believes may be capable of stimulating DNA repair. Based on preclinical studies to date, OXiGENE is now planning the clinical development of these product areas, although the timing and results thereof cannot be determined or assured at this time.

There can be no assurance that the Company's technology will prove effective, that the Company will develop any commercially accepted product, that it will obtain necessary regulatory approvals, that it will be able to enter into strategic alliances or joint ventures or that the terms thereof will be favorable to the Company, or that the Company will be profitable.

Technology Overview

OXiGENE's proprietary technology is based on the relationship between DNA repair and DNA damage as affected by both the operation of ADPRT (a DNA repair enzyme) and cell replication. Normal cells in the human body are constantly subjected to external assault from harmful environmental agents such as the sun's ultraviolet rays, toxic chemicals in the diet and carcinogens such as smoke that are absorbed into the body, as well as from internal assault from metabolic byproducts produced within the cell. These assaults cause damage, or genetic lesions, to the DNA molecules, which contain the genetic blueprint (instructions) for the cell. The cell's structural integrity is dependent on its ability to read and translate those blueprints. Repairing DNA damage is, therefore, essential to a cell's survival. Consequently, the body attempts to counter this constant assault through its genetic mechanisms that monitor genetic lesions to a cell's DNA molecules and repair them enzymatically.

Repair enzymes move constantly along the DNA molecule seeking out genetic lesions and repairing them through a process called "excision repair." One of these enzymes is ADPRT. It identifies a genetic lesion, attaches to the damaged site and engages other enzymes to help in the repair process. The injured portion of the molecule is then removed by enzymatic digestion and additional enzymes repair the damage to the DNA molecule. As DNA is a double helix composed of diametrically opposed strands, the repair enzymes can use the unaffected strand of nucleotides (the class of nucleic acid compounds from which genes are constructed) as a template for determining the correct nucleotides to serve as replacement for the injured portion that has been removed. The process is completed by the repair enzymes, which produce the "complementary twin" and implant it in the previously removed damaged section.

[GRAPHIC]

The excision repair process is selective in that it concentrates on the most active regions of the DNA helix, those containing the genes that are most vital to the cell. Thus, when the rate of damage to a cell is more than the repair system can handle, the repair mechanism first repairs lesions in a cell that occur in frequently read genes, which are the genes that are most important to a cell's day-to-day survival. Damage occurring to inactive or structural portions of the DNA that are not immediately important to a cell's survival is repaired only as time permits, if at all. Therefore, OXiGENE believes that cells become malignant or age by the accumulation of genetic lesions that the DNA repair system has failed to correct properly or in a timely manner.

[GRAPHIC]

The process of DNA repair in the human body

Throughout life, cells replicate by division. Cell division (replication) occurs very quickly and defects are unavoidable. Genetic defects constitute a serious threat to a cell's survival. A persistent genetic defect, or mutation, increases the risk of disease and death. Cancer is a disease in which a mutated tumor cell divides uninterruptedly and in an uncontrolled manner. Normal cells die because tumor cells exhaust nourishment, inhibiting a normal cell's ability to survive and eventually leading to organic malfunctions and death.

Traditionally, cancer treatment has been based on the theory that stopping uncontrolled cell division can halt tumor growth. Both radiation and chemotherapy increase DNA damage in tumorous cells, causing toxicity and cell death. Tumorous cells are known to die by either of two mechanisms, necrosis (death with cell replication) and apoptosis (death without cell replication). OXiGENE's main product line of DNA repair inhibitors are based on N-substituted benzamides, which, the Company believes, cause tumor toxicity primarily by apoptosis. Apoptosis is initiated by cells as an alternative to necrosis, or mutation. The advantage of apoptotic death is that it allows normal living cells to absorb the various components that make up the apoptotic, dying cells without further enzymatic digestion of the cellular components as occurs with necrotic cell death. Accordingly, apoptosis causes cell death

without the many toxic side effects associated with necrosis and enzymatic digestion. This is an important basis for OXiGENE's product development since its goal is to create drugs to counteract cancer that are less hazardous to the individual than those used today.

DNA Repair Inhibition. Cancer therapy typically involves either or both of surgery, to remove the primary tumor, and the application of cytotoxic (cell-killing) agents, such as radiation or chemotherapy, to destroy primary and secondary tumors that are too small or diverse to be removed surgically (called metastases). Nearly all available radiation and chemotherapies work by increasing DNA damage to tumor cells, thus blocking those cells' replication and inhibiting their growth by necrosis or apoptosis, or both, and eventually leading to their death. As tumorous cells replicate substantially more frequently than normal cells, the body's normal DNA repair mechanism tends to counteract the effects of radiation and chemotherapy treatment by promoting the replication, or "regrowth," of the very tumors that have been treated. This process can be prevented by inhibiting the body's normal repair mechanism. Certain chemical compounds are capable of serving as "sensitizers," which supplement the radiation or chemotherapy phase of cancer treatment by inhibiting DNA repair and increasing DNA damage, thereby increasing the efficiency of the cytotoxic agents. Drugs that exhibit sensitizing properties permit an oncologist to elect either to achieve greater results with a given dose of radiation therapy or chemotherapy, or to reduce the level of the cytotoxic agent needed to achieve the same result. Frequently, however, oncologists must cut short therapy because side effects associated with certain sensitizing agents become intolerable before effective tumor killing can occur. The Company believes that its principal products are sensitizers that are capable of inhibiting DNA repair and increasing DNA damage without intolerable side effects when used in conjunction with customary cancer treatments. See "DNA Repair Products and Clinical Trial Program."

DNA Repair Measurement and Stimulation The ADPRT enzyme is an important enzyme in the DNA repair process because it recognizes DNA damage and alters certain proteins in the damaged site, enabling the other repair enzymes to gain access to that site and to complete the excision repair process. Therefore, if an individual's level of ADPRT is high, DNA damage is being removed efficiently, and if an individual's level of ADPRT is low, DNA repair is being inhibited and DNA damage will accumulate. Consequently, by measuring individual levels of ADPRT, the Company believes it is possible to determine how well the DNA repair process is functioning in preventing accumulated DNA damage. OXiGENE believes that knowledge of DNA repair activity may be useful for monitoring or screening individuals for susceptibility to cancer, immune deficiencies, chemotherapeutic drug resistance and the success or failure of chemopreventive treatment.

OXiGENE believes that knowledge of the body's metabolic function and its related process known as "oxidative stress," in which a small number of metabolic "mistakes" occur and cause the formation of certain intermediates that damage DNA, and knowledge of the body's inflammatory response that causes a decline in DNA repair may lead to the development of drugs that can stimulate DNA repair. Drugs of that type, the Company believes, could reduce a person's susceptibility to cancer and certain diseases associated with the aging process by increasing net DNA repair capacity.

Although the Company has conducted extensive preclinical cell and animal research into each of the areas of DNA repair measurement and DNA repair stimulation, and is currently planning the early stages of their clinical development, there can be no assurance that any drugs related to either of these areas can or will be developed by the Company. See "-- DNA Repair Product and Clinical Trial Program."

Product Development and Marketing Strategy

The Company's goal is to develop products that enhance the efficacy of existing forms of cancer treatment, such as radiation and chemotherapy, and improve a patient's quality of life by selectively inhibiting the DNA repair function of, and increasing DNA damage in and death of, tumor cells. The Company intends to continue and expand its ongoing clinical trial program in Europe and commence research and clinical trials in the United States. The Company's policy has been to establish relationships with universities, research organizations and other institutions in the field of oncology. The Company intends to further strengthen these relationships, rather than expand its in-house research and clinical staff. Although the Company plans to market its products directly in certain European countries, it has had preliminary discussions with unaffiliated pharmaceutical companies regarding strategic alliances or joint ventures for the manufacturing and marketing of its products in the United States, the Far East and elsewhere. To date the Company has not entered into any such alliances or ventures.

Currently, the Company has collaborative arrangements with the University of Lund in Lund, Sweden, the Strang Cancer Prevention Center in New York, New York, New York University in New York, New York, Gray Laboratories in Middlesex, United Kingdom, Aarhus University in Aarhus, Denmark, CNRS in Strassbourg, France and Georgetown University in Washington, D.C. See "--Collaborative Arrangements."

In particular, the Company believes that its collaborations with the University of Lund enable it to conduct trials of its products in an environment offering a homogenous patient population at less cost and more rapidly than the Company could achieve in the United States. The University of Lund has historically provided, and continues to provide, the Company with access to clinical trial facilities, patients and research facilities. Additionally, the Company benefits indirectly from certain research grants received by the University of Lund.

OXiGENE's DNA Repair Products and Clinical Trial Program

DNA Repair Inhibiting Products

OXiGENE has discovered that certain compounds in the family of N-substituted benzamides are capable of inhibiting ADPRT-modulated DNA repair and selectively reacting with radiation to cause additional DNA damage exclusively in the treated area. OXiGENE believes that this selectivity is due to tumor cells exhibiting increased DNA repair activity as compared to normal cells, rendering them more sensitive to DNA repair inhibition and death by apoptosis. The Company believes, on the basis of its research activities to date, that its principal products, Sensamide(TM) and Neu-Sensamide(TM), act as selective, targeted sensitizers of tumor tissue and sensitize radiation exclusively inside the treated area without producing significant toxic side effects outside the treated area.

Oxi-104, the Company's newest compound, is not based on metoclopramide and, therefore, although it is a N-substituted benzamide it is unlike Sensamide(TM) or Neu-Sensamide(TM). The Company believes that Oxi-104 alone can induce tumor growth-inhibiting and tumor-killing effects. Oxi-104 has been designed with a molecular structure that, the Company believes, will reduce side effects while maintaining the sensitizing properties of other N-substituted benzamides. For the Company's two radiation sensitizer products, Sensamide(TM) and Neu-Sensamide(TM), both of which are based on N-substituted benzamide known as metoclopramide, the limiting doses are determined by their central nervous system (CNS) side effects. By comparison, Oxi-104 has not yet shown any CNS side effects.

The current emphasis of the Company's clinical program is on evaluating the safety and efficacy of Sensamide(TM) and Neu-Sensamide(TM) as sensitizing agents in combination with radiation therapy, with the goal of obtaining product labeling for Neu-Sensamide(TM) as a radiation sensitizer not limited to a specific form of cancer. In the middle of 1994, the Company commenced a study of Sensamide(TM) in patients with inoperable non small-cell lung cancer ("NSCLC"). In the fourth quarter of 1996, the Company intends to commence a Phase III study of Neu-Sensamide(TM) in patients with NSCLC. The combined results of the Sensamide(TM) and Neu-Sensamide(TM) studies will serve as the basis of the Company's NDA for Neu-Sensamide(TM) as a radiation sensitizer for NSCLC. In August 1996, the Company commenced a Phase I/II study of Neu-Sensamide(TM) in patients with glioblastomas, a highly malignant form of brain cancer. The FDA has advised the Company that if the Company is able to demonstrate the clinical efficacy of Neu-Sensamide(TM) in conjunction with radiation therapy in two different forms of cancer under controlled study conditions, and in two or three additional forms of cancer under uncontrolled study conditions, OXiGENE will receive product approval for Neu-Sensamide(TM) as a radiation sensitizer for all cancer indications treated with radiation.

OXiGENE is collaborating with ILEX, a drug development company based in San Antonio, Texas, on the development of Oxi-104. ILEX will conduct pre-clinical development work through the filing of an IND on a contract basis. This work will include pharmacokinetics studies, toxicology studies in accordance with CGLP standards, process development, scale-up/manufacturing for anticipated clinical trial needs under FDA current good manufacturing practice ("cGMP") standards, analytical development, and compilation and submission of an IND. OXiGENE anticipates having a pre-IND meeting with the FDA regarding Oxi-104 in February 1997.

The Company currently anticipates commencing a Phase I clinical trial of Oxi-104, after the filing of an IND with the FDA in the second quarter of 1997. Based on preliminary results, OXiGENE believes it can demonstrate that Oxi-104 alone can induce tumor growth-inhibiting and tumor-killing effects.

A summary of the clinical studies related to the Company's products that are currently under development is set forth in the following table (which is supplemented further by the more detailed information contained in Appendix I hereto):

Summary of OXiGENE's Clinical Program

Study	Phase	Total patients	Randomization	Treatment Assignment	Status
Sensamide(TM) in NSCLC	I/II	23	None	All patients on Sensamide(TM) (i.v.)	Published 1995
Sensamide(TM) in NSCLC	II/III	226	Control	Sensamide(TM) (i.v.) + radiation - 113; Radiation only - 113	Ongoing; greater than 180 patients as of September 1996; final report third quarter 1997

Study	Phase	Total patients	Randomization	Treatment Assignment	Status
Comparative study of Sensamide(TM), Neu-Sensamide(TM) and Placebo (healthy volunteers)	I	19	Placebo, double-blind cross-over	Placebo-12; Sensamide(TM) (i.v.) -15; Neu-Sensamide(TM) (i.v.) - 13; Neu-Sensamide(TM) (i.m.) - 13	Final report September 1995
Neu-Sensamide(TM) in NSCLC	III	226	Control	Neu-Sensamide(TM) (i.m.) + radiation - 113; Radiation only - 113	Estimated start 4th quarter 1996
Neu-Sensamide(TM) in glioblastomas	I/II	15	None	Neu-Sensamide(TM) (i.m.) - 15	Ongoing; 2 patients as of September 1996
Oxi-104 in refractory cancer (solid tumors)	I	15	None	All patients on Oxi-104	Planning phase

Certain terms and abbreviations used in the foregoing table are explained in the Glossary on page 48.

DNA Repair Measuring Products

ADPRT Assay Products. The Company believes that knowledge of DNA repair activity can be applied to monitor or screen individuals for susceptibility to cancer, immune deficiencies, chemotherapeutic drug resistance and the success or failure of chemo-preventive treatments. Studies have shown that DNA repair capacity varies from one individual to another. OXiGENE has quantified individual levels of ADPRT as a DNA repair estimate, and holds an exclusive license, which expires in 2011, to an issued Canadian patent and pending U.S., European and Japanese patent applications covering an ADPRT diagnostic test that measures ADPRT levels in white blood cells. The Company has determined that a simple serum-based test can give a reliable surrogate indication of the level of ADPRT in white blood cells, quickly and at low cost. OXiGENE believes that such a test, for which it filed a U.S. patent application in October 1994, may be commercially acceptable, although there can be no assurance in that regard.

The New York University Department of Environmental Medicine and the Center of Aids Research have conducted an investigation using OXiGENE's assay for measuring ADPRT levels (i.e., the serum thiol-based surrogate test) on 133 patients who were intravenous narcotic drug users and were infected with the HIV virus that causes AIDS. This repair assay assesses DNA repair activity by measuring total serum thiol levels. Preliminary results indicate that this assay may be effective in monitoring the progression of HIV-related diseases. The Company believes that measuring a person's immune function through DNA repair activity may be a better indication of HIV-related disease progression and, consequently, survival than more commonly used indicators such as CD4 cell counts.

The Company intends to pursue the development of a more-cost-effective, easy-to-administer version of the assay for commercialization.

DNA Repair Stimulating Products

Cancer, as well as the general deterioration of the body leading to aging disorders connected to immunity, is generally recognized in the medical field as a mutational disease arising from the build-up of genetic damage in unrepaired areas of DNA. By enhancing DNA repair in the inactive areas of the DNA structure, genetic damage build-up can be reduced with a corresponding reduction in cell mutation. OXiGENE research has to date concentrated on identifying compounds that can slow the natural production of DNA repair inhibitors produced by the body when inflammatory cells are activated as a first line defense against infections or cancer cells. By blocking this natural production of DNA repair inhibitors by inflammatory cells, the Company has, through its tests to date, demonstrated that a net increase in DNA repair capacity can be achieved.

The Company has developed a screening program based on DNA repair measurements of in vivo-exposed spleen and cells. The Company has identified a new mixture of naturally-occurring compounds that it believes is capable of stimulating DNA repair, and which is currently under evaluation by the Company in cell and animal models to optimize enhancement of DNA repair. OXiGENE has filed an international (PCT) patent application for this mixture of DNA repair stimulators.

The Company believes that DNA repair enhanced compounds may be used to supplement, or under certain circumstances replace, chemopreventive agents for cancer already in use, such as Tamoxifen(TM), as well as chemopreventive agents in various stages of development. Any DNA repair enhancer drugs developed by OXiGENE will be based on naturally occurring compounds, rather than synthetic analogs. Consequently, the Company believes that they would be less inherently toxic than newly-synthesized chemopreventive agents already in clinical trials. However, there can be no assurance that the Company will be able to develop any such drug, or if developed, that such drug could be successfully marketed.

Drug Development and Regulatory Processes

Research initially involves optimization of leading chemical structures into leading compounds. Once a leading compound has been identified, the preclinical phase commences. In that phase, certain selected compounds are tested for therapeutic potential in a number of animal models, with the objective of characterizing the investigated compounds in relation to existing treatment and getting a first indication of the compounds' development potential. Successful preclinical work may lead to the filing of an IND with the relevant national regulatory authorities. The IND is a permission to administer the compound to humans in clinical trials. Several years of research and testing generally are necessary before an IND can be obtained and clinical development commence.

The clinical development of new drugs is subject to approval by the health authorities in individual countries. The duration of the clinical phase requirements among countries vary considerably. For life threatening and severely debilitating conditions where no satisfactory treatment currently exists, however, it is possible to accelerate the development process in the United States through the "Accelerated Drug Approval Program." In other countries, the trial process for drugs targeted toward life threatening

diseases is shortened by lower requirements regarding the patient sample size required to be met in the trials.

The time periods mentioned below are indications only and may vary. Upon successful completion of the development program, a New Drug Application ("NDA") may be submitted to the authorities, and upon approval the product may then be marketed. Even thereafter, however, a company will remain subject to regulatory review.

Phase I. The purpose of Phase I studies is to evaluate the toxicity of the tested compound and to establish how the tested compound is tolerated and decomposed in the human body. Phase I clinical trials traditionally involve tolerance, absorption, metabolism and excretion studies in a small group of healthy individuals. Phase I may last up to one year.

Phase II. Phase II marks the beginning of clinical trials on a limited number of patients and permits the determination of dose levels in relation to effect and tolerance. The trials also seek to establish the most effective route of administration. Trials are conducted on a small sample of carefully monitored patients. Phase II may last up to two years.

Phase III. Phase III is extensive clinical trials in large samples of patients. The number of patients in a Phase III trial program depends to a great extent on the clinical indications that the drug addresses. Trials are often double-blinded and involve a detailed statistical evaluation of test results. The compound is tested against placebo and existing treatment, if such treatment is available. Production is upscaled, and further evaluation of the durability and stability of the compound takes place. Phase III may last several years and is the most time-consuming and expensive part of a clinical trial program.

OXiGENE, like other pharmaceutical companies, will be subject to strict controls covering the manufacture, labeling, supply and marketing of any products it may develop and market. Further, OXiGENE is subject to controls over clinical trials of its potential pharmaceutical products. The most important regulation is the requirement to obtain and maintain regulatory approval of a product from the relevant regulatory authority to enable it to be marketed in a given country.

The regulatory authorities in each country may impose their own requirements and may refuse to grant, or may require additional data before granting, an approval even though the relevant product has been approved by another authority. The United States and European Union ("EU") countries have very high standards of technical appraisal and, consequently, in most cases a lengthy approval process for pharmaceutical products. The time required to obtain such approval in particular countries varies, but generally takes from six months to several years from the date of application, depending upon the degree of control exercised by the regulatory authority, the duration of its review procedures and the nature of the product. The trend in recent years has been towards stricter regulation and higher standards, but accelerated approval processes exist in the United States and elsewhere for so-called breakthrough drugs for patients with life-threatening or serious diseases.

In the United States, the primary regulatory authority is the FDA. In addition to regulating clinical procedures and processes, the FDA investigates and approves market applications for new pharmaceutical products and is responsible for regulating the labeling, marketing and monitoring of all such products, whether marketed or under investigation.

In Europe, the European Committee for Proprietary Medicinal Products provides a mechanism for EU-member states to exchange information on all aspects of product licensing and assesses license applications submitted under two different procedures (the multistate and the high-tech concentration procedures). The EU has established a European agency for the evaluation of medical products, with both a centralized community procedure and a decentralized procedure, the latter being based on the principle of mutual recognition between the member states.

Research and Development and Collaborative Arrangements

The Company's research and development programs are generally pursued in collaboration with academic and other institutions. Under current arrangements, the Company is not required to pay any royalties or licensing fees for technology and products developed with financial assistance from or at the facilities of such agencies and institutions, except for a 5% gross royalty payable in respect of an exclusive worldwide license of the patent covering the ADPRT Diagnostic Assay. There can be no assurance that royalties or fees, potentially material as to their amount, will not be required under any future arrangements.

The Company incurred approximately $0.9 million, $1.8 million and $2.8 million in research and development expenses in the years ended December 31, 1993, 1994 and 1995, respectively. For the six month period ended June 30, 1996, such expenses were approximately $2.4 million. Substantially all of these amounts represent external research and development expenditures.

Swedish Cancer Society. In 1992, the Swedish Cancer Society awarded Dr. Ronald Pero, in his capacity as a faculty member of the University of Lund, a three-year grant for a total of approximately $0.3 million to investigate benzamide and nicotinamide analogs relating to Sensamide(TM) as radiosensitizers. This grant was renewed in 1995 for a one year period totaling approximately $0.2 million. The Company was not the recipient of any of these funds. The study's principal objective was to determine what chemical features give benzamide/nicotinamide compounds multiple forms of radiosensitizing action.

In 1992, Dr. Pero, in his capacity as a collaborating faculty member of the University of Lund, was awarded another Swedish Cancer Society research project, (principal investigator Professor Goran Berglund), for approximately $0.4 million over a three-year period, to direct the biological bank and biomarker program portion of the Malmo Diet Study. This project has had its funding renewed until October 1996, the anticipated date of completion of patient enrollment. The Company was not the recipient of any of these funds. The Malmo Diet Study, sponsored in part by the World Health Organization, involves a large ongoing control case study in which individuals between the ages of 46 years and 64 years, living in the city of Malmo, Sweden, have been invited to participate in a study designed to evaluate dietary factors as causative agents for cancer. The city of Malmo was selected as the site of this study because of the historically high incidence of cancer in its relatively homogeneous population.

University of Lund/Strang Cancer Prevention Center Agreement. In 1987, the University of Lund entered into a research collaboration agreement with the Strang Cancer Prevention Center in New York City. The purpose of the collaboration is to develop biomarkers and to contribute to the basic knowledge of DNA repair in relation to human diseases. The program is conducted primarily in the Wallenberg Laboratory of the University of Lund. Dr. Pero was appointed to head this international collaborative effort and was awarded professorial privileges and laboratory space, which is currently being used by Dr. Pero and his research colleagues. Initially, Dr. Pero's salary was paid by the Strang Cancer Prevention

Center, but in 1990 that responsibility was assumed by the Company. The Wallenberg Laboratory specializes in providing high quality research space to selected research projects being developed within the academic community. Currently, the program focuses its research efforts on immunology and tumor biology, areas directly related to the Company's principal technology development. Most of the Company's preclinical and clinical research is carried out at the Wallenberg Laboratory, financed by research grants and contracts. The University of Lund has not claimed any proprietary interest in the products developed by the Company there.

Preventive Medicine Institute. Pursuant to an agreement dated October 7, 1991 (the "PMI License Agreement"), between a predecessor of the Company and Preventive Medicine Institute, a New York not-for-profit corporation affiliated with the Strang Cancer Prevention Center in New York, New York, the Company received an exclusive, worldwide license to patent rights covering the ADPRT Diagnostic Assay, which license expires on October 7, 2011. The PMI License Agreement requires the Company to pay a royalty equal to 5% of the total amount of any revenues received by the Company in respect of the ADPRT Diagnostic Assay with a total maximum payment of $1 million. To date, the Company has made no royalty payments as this product has not been commercially developed.

New York University Medical Center. In 1990, Dr. Pero was appointed as adjunct professor at NYU Medical Center, and was provided with certain laboratory space. During 1995, the Company continued to use the space to conduct research using its diagnostic tests as biomarkers of hazardous environmental exposures, cancer susceptibility and AIDS prognosis while continuing its development of a cost effective and simple surrogate version of the assay (test) for commercialization. In 1995, the Company granted to New York University $25,000 for a study entitled "Retrospective Trial of N-Cloroamine as a Prognostic Indicator of HIV Disease," which is related to the Company's diagnostic assay.

Professor Myron K. Jacobson, The College of Pharmacy, University of Kentucky. Professor Jacobson is the Chairman of the Division of Medicinal Chemistry and Pharmaceuticals, College of Pharmacy, University of Kentucky, Lexington, Kentucky. In November 1994, the Company entered into a consulting agreement with Professor Jacobson, under which he will assist the Company's core research and development efforts in the DNA repair area and ADP-ribosylation. Dr. Jacobson is paid a $5,000 per annum consulting fee and was granted options to acquire 5,000 shares of the Company's Common Stock at an exercise price of $5.50 per share. The options fully vest on December 31, 1996, provided Dr. Jacobson remains a consultant to the Company through that date, and terminate in 2004.

Dr. Michael Horsman, The Danish Cancer Society, Aarhus, Denmark. Dr. Horsman entered into a consulting agreement with the Company in November 1994, under which he will assist the Company's research programs in determining certain relations between the Company's drugs and radiation. Dr. Horsman is paid a $5,000 per annum consulting fee.

Dr. Claus Moller, IPC Nordic A/S, Copenhagen, Denmark. IPC Nordic A/S is a pharmaceutical consulting company based in Copenhagen, Denmark, which specializes in supporting European clinical trials and distribution of drugs in Scandinavia. Dr. Moller, the President of IPC Nordic, is a director of the Company, and serves as the Company's Chief Medical Officer. Dr. Moller is responsible for the coordination of the Company's European clinical trials as well as the everyday operation of the Company's Swedish subsidiary. In addition to 5000 director options, exercisable at $6.00, Dr. Moller received options to purchase 30,000 shares of the Company's Common Stock, at an exercise price of

$5.50 per share, in March 1994, all of which are fully vested. An additional 70,000 options were granted to Dr. Moller in June 1995 at an exercise price of $6.375. These options vest in three equal annual installments on July 1, 1996, 1997 and 1998, provided Dr. Moller is rendering services to the Company on those dates, and will terminate in 2005.

Dr. David J. Chaplin, the Gray Laboratory, Middlesex, United Kingdom. Dr. Chaplin is Head of the Tumour Microcirculation Group at the Gray Laboratory Cancer Research Trust Mount Vernon Hospital. Under an agreement signed in May 1995 Dr. Chaplin retains his position at the Gray Laboratory but is also employed by OXiGENE as Vice President for Basic Research, Sensitizer Program and serves as the Secretary of the Company's Scientific Advisory Board. Dr. Chaplin is responsible for planning preclinical studies at the Gray Laboratory and, in conjunction with Dr. Pero, defining and coordinating radio- and chemosensitizing studies of the Company's proprietary compounds at other research centers. Dr. Chaplin is paid $30,000 per annum and was granted options to purchase 30,000 shares of Common Stock, at an exercise price of $5.375 per share, vesting in three installments, on June 1, 1995, 1996, and 1997.

Dr. Sylviane Muller, Institut de Biologie Moleculaire et Cellulaire, Strasbourg, France. In November 1995 the Company signed a one year research agreement with Dr. Muller to perform a collaborative study on the "Preparation of Antibodies Reacting Selectively with the Oxidized Zinc Finger Region of Poly-ADPRT." The Company will pay Le Centre National De La Recherche Scientifique, the parent organization of the Institut de Biologie Moleculaire et Cellulaire, $35,000 for this study.

Dr. Mark Smulson, Georgetown University, Washington D.C. The Company has entered a research agreement with Georgetown University, pursuant to which Dr. Smulson will conduct research to clarify the interference of N-substituted benzamides with the functioning of ADPRT and related enzymes. Georgetown University receives $72,000 for this study.

Patents and Trade Secrets

Certain of OXiGENE's current therapeutic products are based on available compounds that are produced by others. The Company anticipates that any products it develops hereafter may include or be based on the same or other compounds owned or produced by unaffiliated parties, as well as synthetic compounds it may discover. Although the Company expects to seek patent protection for any compounds it discovers, there is no assurance that any or all of them will be subject to effective patent protection. Further, the development of regimens for the administration of pharmaceuticals, which generally involve specifications for the frequency, timing and amount of dosages, has been, and the Company believes will continue to be, important to the Company's efforts, although those processes, as such, may not be patentable.

Patent Protection

It is the Company's policy to seek patent protection in the United States and elsewhere throughout the world. Primarily because of differences among patent laws in various jurisdictions, the scope of, and hence the protection afforded by, any patents OXiGENE may receive may vary from place to place even though they relate essentially to the same subject matter.

The patent position of firms in the Company's industry generally involves highly complex legal and other issues, resulting in both an apparent inconsistency regarding the breadth of claims allowed in United States patents and general uncertainty as to their legal interpretation and enforceability.

Accordingly, there can be no assurance that patent applications owned by the Company will result in patents being issued or that, if issued, the patents will afford competitive protection.

Further, there can be no assurance that products or processes developed by the Company will not be covered by third party patents, in which case continued development and marketing of those products or processes could require a license under such patents. OXiGENE cannot assure that if a legal action were to be brought against the Company on the basis of any third party patents, such action would be resolved in the Company's favor. An unfavorable result against the Company could result in monetary damages and injunctive relief. Even a favorable result could cause expenditure of substantial monetary and other resources in connection with the Company's defense against any such action.

Granted Patents and Pending Applications. The following is a brief description of the Company's current patent position, both in the United States and abroad. As U.S. patent applications are maintained in secrecy until patents issue and because publication of discoveries in the scientific or patent literature often lags behind actual discoveries, OXiGENE cannot be certain that it was the first creator of inventions covered by its pending applications or that it was the first to file patent applications for those inventions.

As of October 1, 1996, the Company is the assignee of four granted U.S. patents, four pending U.S. patent applications, and of granted patents and/or pending applications in other countries (and/or international applications designating other countries) corresponding to three of the granted U.S. patents and two of the pending U.S. applications. Two of the U.S patents issued in 1996, and three of the pending U.S. applications were filed in 1996, of which one is a provisional application and another is a U.S.-designating international application (also designating other countries) based on a U.S. provisional application filed in 1995.

Specifically, the Company is the assignee of a U.S. patent, granted April 20, 1993, for glutathione-s-transferase Mu as a measure of drug resistance, covering a test for resistance to nitrosoureas (a class of chemotherapeutic agents). In addition, the Company is the assignee of a U.S. patent, granted August 23, 1994, for tumor or cancer cell-killing therapy (covering methods of using N-substituted benzamides including Sensamide(TM) and Neu-Sensamide(TM) as radio- and chemosensitizers), and of granted patents in Australia, Canada, Europe (designating 13 countries), Ireland, Israel, Mexico and South Africa and an allowed patent application in Russia (as well as pending applications in Denmark and Japan) corresponding thereto. The Company is also the assignee of two U.S. patents, both granted October 1, 1996, for methods of administering and pharmaceutical formulations containing N-substituted benzamides and/or acid addition salts thereof (covering, e.g., Neu-Sensamide(TM)) and for methods of administering phenothiazines and/or acid addition salts thereof, and of a granted South African patent and pending European and other foreign applications corresponding to these two new U.S. patents. The Company's four pending U.S. applications and international counterparts cover further methods of testing or treatment and compositions, including the Oxi-104 product.

Moreover, the Company is the exclusive licensee of a U.S. patent, granted January 9, 1996, for a diagnostic test involving measurements related to the cellular process of DNA repair and drug resistance, and is the exclusive licensee of corresponding granted Canadian and European patents and a corresponding pending Japanese patent application. The owner of the licensed patents and application is Preventive Medicine Institute.

Trade Secrets and Technological Know-How. While the Company generally will pursue a policy of seeking patent protection to preserve its proprietary technology, it also has and will continue to rely on

trade secrets, unpatented proprietary information and continuing technological innovation to develop and maintain its competitive position. There can be no assurance, however, that others will not independently develop substantially equivalent proprietary information and techniques or otherwise gain access to such or equivalent trade secrets, proprietary information or technology or that OXiGENE can meaningfully protect its rights to such secrets, proprietary information and technology.

OXiGENE requires its employees and Scientific Advisory Board members to enter into confidentiality agreements with the Company. Those agreements provide that all confidential information developed or made known to the individual during the course of the relationship is to be kept confidential and not to be disclosed to third parties, except in specific circumstances. In the case of employees, the agreements also provide that all inventions conceived by such employees shall be the exclusive property of OXiGENE. There can be no assurance, however, that any such agreement will provide meaningful protection for the Company's trade secrets in the event of unauthorized use or disclosure of such information. Moreover, although the Company has confidentiality agreements with the institutions that perform its preclinical and clinical tests, the Company has no such agreements with the employees of such institutions, and there can be no assurance that these employees will abide by the terms of such agreements.

Competition

The industry in which the Company is engaged is characterized by rapidly evolving technology and intense competition. The Company's competitors include, among others, major pharmaceutical and biotechnology companies, many of which have financial, technical and marketing resources significantly greater than those of the Company. In addition, many of the small companies that compete with the Company have also formed collaborative relationships with large, established companies to support research, development and commercialization of products that may be competitive with those of the Company. Academic institutions, governmental agencies and other public and private research organizations are also conducting research activities and seeking patent protection and may commercialize products on their own or through joint ventures.

The Company is aware of a number of companies engaged in the research, development and testing of new cancer therapies or ways of increasing the effectiveness of existing therapies. Such companies include, among others, Bristol-Meyers Squibb Co., Burroughs Welcome, Eli Lilly and Ciba-Geigy Ltd., some of whose products have already received regulatory approval or are in later stages of clinical trials. The Company is also aware of companies engaged in the research, development and testing of diagnostic assays for cancer, including Introgen Therapeutics, Anti Cancer, Transgene and Medarex. There are other companies that have developed or are in the process of developing technologies that are, or in the future may be, the basis for competitive products in the field of cancer therapy or other products the Company intends to develop. Some of those products may have an entirely different approach or means of accomplishing the same desired effects as the products being developed by the Company, such as gene transfer therapy, immunotherapy and photodynamic therapy. There can be no assurance that the Company's competitors will not succeed in developing technologies and products that are more effective, safer or more affordable than those being developed by the Company.

Radiation therapy has been increasingly accepted as a complement to chemotherapy in a multi-modality treatment of NSCLC. Further, a number of organizations have developed new chemotherapeutic regimens that are under study in late-stage clinical trials. To the best knowledge of the Company, however, none of the foregoing is, and none of the new forms of non-surgical cancer treatment currently

under development appears to be, directly competitive with Sensamide(TM) or Neu-Sensamide(TM) as a sensitizer that has entered Phase II/III study.

As the Company's products complement and enhance radiation therapy and chemotherapy as applied to NSCLC, the Company believes that enhancements in those treatments, particularly if they lead to their successful application, could increase the market for the Company's products, although there can be no assurance in this regard. Moreover, if the Company's products also complement new cancer treating therapies, the use of these new therapies might also expand the Company's market.

The Company expects that if any of its products gain regulatory approval for sale they will compete primarily on the basis of product efficacy, safety, patient convenience, reliability, price and patent position. The Company's competitive position also will depend on its ability to attract and retain qualified scientific and other personnel, develop effective proprietary products and implement joint ventures or other alliances with large pharmaceutical companies in order to jointly market and manufacture its products.

Employees

The Company's policy has been, and continues to be, to maintain a relatively small number of executives and other employees and to rely as much as possible on consultants and independent contractors for its research and clinical trials. As of August 30, 1996, the Company had eleven full-time employees, of which seven were engaged in research and development and clinical trial evaluations. Most of the Company's preclinical and clinical tests are subcontracted and performed at the University of Lund, Sweden, and at other European centers, with the assistance of CATO Research, Ltd., Durham, North Carolina, an independent clinical research firm, IPC Nordic A/S, a Danish pharmaceutical consulting firm, Charterhouse Ltd. The Royal Masonic Hospital, a hospital in London, U.K. and ILEX Oncology Inc., a contract research organization in Austin, Texas.

Properties

The Company subleases its executive offices in New York, New York, currently at an annual rent of approximately $41,000. The lease expires on December 31, 1996. The Company believes that it can readily find executive office space suitable to its needs and at a reasonable cost should it be required to do so. Recently, the Company opened an executive office in Stockholm, Sweden, in anticipation of the listing of the SDSs on the Stockholm Stock Exchange. The Stockholm office is subleased, at an annual rate of approximately $25,000, under an arrangement that expires on September 1998. The Stockholm office lease may be terminated at any time upon nine months written notice. The Company also leases space at the Ideon Research Park in Lund, Sweden. The lease expires on January 31, 1998, and the annual rent is approximately $19,500. The Company does not own or lease any laboratories or other research and development facilities.

Executive Officers and Directors

The executive officers and directors of the Company are as follows:

Name	Age	Position
Bjorn Nordenvall, M.D., Ph.D.....	44	Chief Executive Officer, President and Chairman of the Board of Directors
Claus Moller, M.D., Ph.D.....	34	Chief Medical Officer and a Director
Ronald W. Pero, Ph.D.....	55	Chief Scientific Officer and a Director
Marvin H. Caruthers.....	56	Director
Michael Ionata.....	45	Director
Bo Haglund.....	43	Chief Financial Officer
M. Andica Kunst.....	35	Vice President and Corporate Secretary

Bjorn Nordenvall, M.D., Ph.D., 44, was appointed as a director in March 1995, and became the Company's President and Chief Executive Officer in June 1995. Dr. Nordenvall serves on the Company's Audit Committee. Dr. Nordenvall is a specialist in general surgery and, from 1987 to September 1996, was President of Sophiahemmet AB, a Stockholm-based hospital. During 1983 and 1984, Dr. Nordenvall was President of Carnegie Medicine AB, Stockholm, Sweden, a biotechnology company, and from 1977 through 1985, he practiced surgery at Danderyd Hospital, Stockholm. From 1984 through 1986, Dr. Nordenvall served as a consultant to D. Carnegie AB, a Swedish investment banking company, and, since 1984, he has been a consultant to Skandia Insurance Company.

Claus Moller, M.D., Ph.D., 34, was appointed as a director in March 1995. Since April 1, 1994, Dr. Moller has served as a consultant to the Company, responsible for coordinating its European clinical trials. Dr. Moller is the President and a principal shareholder of IPC Nordic A/S, a Danish consulting firm. See "- Certain Relationships and Related Transactions." From 1989 to 1994, Dr. Moller was Medical Director for Synthelabo Scandinavia A/S and from 1983 to 1992, he was involved in cell biology and biomedical research at the University of Copenhagen, Denmark.

Ronald W. Pero, Ph.D., 55, is a co-founder of OXiGENE, and has been a director and the Company's Chief Scientific Officer since its inception. From November 1993 to June 1995, Dr. Pero also served as President of the Company. Dr. Pero specializes in the field of DNA repair and its relation to cancer treatment, and directs and coordinates the Company's research and development efforts. Dr. Pero has been a fellow of the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, a director of the Division of Biochemical Epidemiology at the Strang Cancer Prevention Center in New York City, and currently holds faculty positions at both New York University Medical Center and the University of Lund in Lund, Sweden, where he is a Professor of Molecular Ecogenetics. Dr. Pero is also a member of the American Association of Science, New York Academy of Sciences,

International Preventive Oncology Society, European Society for Therapeutic Radiation Oncology and The American Association of Cancer Research, as well as serving as Scientific Director of the Board of Trustees of the Swedish American Research Foundation. Dr. Pero has published more than 175 manuscripts related to his research.

Marvin H. Caruthers, Ph.D., 56, was elected as a director at the Company's 1996 Annual Meeting of Stockholders, and serves on the Company's Compensation Committee. Dr. Caruthers is a Professor of Chemistry and Biochemistry at the University of Colorado, Boulder, Colorado, whose research in nucleic acid chemistry resulted in new methods for the chemical synthesis of DNA. Dr. Caruthers is a scientific co-founder of, and serves as a consultant to, Amgen Incorporated, a biotechnology company engaged in the development of products derived from gene synthesis capabilities, and is a scientific co-founder of Applied Biosystems Incorporated, a biotechnology company engaged in the development of DNA synthesizers and protein sequencers and a division of Perkin/Elmer Inc. Dr. Caruthers also serves on the board of directors of BioStar, Inc., a biotechnology company, and Skandigen AB, a Swedish biotechnology company ("Skandigen"). Dr. Caruthers, who is a member of the United States National Academy of Sciences and the American Academy of Arts and Sciences, has published more than 140 manuscripts related to his research.

Michael Ionata, 45, was appointed as a director in October 1995, and serves as Chairman of the Company's Compensation Committee. Mr. Ionata is Director of Corporate Finance of Nordberg Capital Inc., an investment banking firm based in New York, the directors, officers and key employees of which own, collectively, 72,800 shares of OXiGENE Common Stock. From May 1983 to May 1991, Mr. Ionata worked in corporate finance and venture capital management at Den Norske Bank in New York. Prior to joining Den Norske Bank, Mr. Ionata worked for Coopers & Lybrand LLP specializing in valuations, cost-benefit analysis and restructurings. Mr. Ionata is currently a director of C.E.L. Industries Poland, a restaurant company, and was a director of Skandigen.

Bo Haglund, 43, was appointed Chief Financial Officer in August 1996. From January 1992 to August 1996, Mr. Haglund was employed by Carnegie in various capacities, most recently heading its London operations, focusing on the marketing of Scandinavian and emerging market stock to U.K. investors. Prior to joining Carnegie, from November 1990 to January 1992, Mr. Haglund was executive vice president and chief financial officer of Swedish Exploration Consortium AB, a Swedish publicly-traded company engaged in oil and gas exploration. From January 1988 to October 1990, Mr. Haglund was vice president finance of Cool Carriers AB and from April 1982 to December 1987, he was chief financial officer of Gulf Agency Group.

M. Andica Kunst, 35, was appointed Vice President and Corporate Secretary in July 1996. Ms. Kunst is responsible for the Company's legal and administrative affairs. Prior to joining the Company, Ms. Kunst was an attorney with the New York City law firm of Battle Fowler LLP, the Company's outside general counsel in the United States. Ms. Kunst holds a LL.M. in Corporate Law from New York University School of Law, a Masters in International Affairs from The George Washington University and degrees in Dutch and International Law from the University of Amsterdam, Amsterdam, The Netherlands.

Board of Directors Committees and Meetings

The Board of Directors has two standing committees: the Audit Committee and the Compensation Committee. Currently, the Company has no Executive Committee.

The Audit Committee reviews, with the Company's independent auditors, the scope and timing of their audit services and any other services they are asked to perform, the auditor's report on the Company's financial statements following completion of their audit and the Company's policies and procedures with respect to internal accounting and financial controls. In addition, the Audit Committee makes annual recommendations to the Board of Directors regarding the appointment of independent auditors for the ensuing year. The Audit Committee currently consists of Messrs. Nordenvall (Chairman) and Ionata.

The Compensation Committee reviews and makes recommendations to the Board of Directors regarding the salaries, benefits and bonuses of the Company's officers. In addition, the Compensation Committee reviews and advises on general policy matters relating to employee compensation and benefit matters, and administers the OXiGENE 1996 Stock Incentive Plan. The Compensation Committee currently consists of Messrs. Ionata (Chairman) and Caruthers, the Company's two non-employee directors.

Advisors to Board of Directors

Following the Company's 1996 Annual Meeting of Stockholders, Professor Hans Wigzell and Dr. Peter Sjostrand were appointed as advisors to the Board of Directors. In that capacity they attend meetings of, although they do not vote on any matters submitted to, the Board of Directors for approval, and regularly provide expertise and advice to the Company in several areas.

Peter Sjostrand, M.D., serves on the board of directors of Pharmavision 2000 AG, a publicly-traded Swiss investment company focusing on the health care industry, and is the chairman of the board of directors of Trygg-Hansa, a publicly-traded Swedish insurance company. From 1975 through 1993, Dr. Sjostrand was employed by Astra AB, a publicly-traded Swedish pharmaceutical company, most recently as its executive vice president and chief financial officer. In addition to a medical degree from The Karolinska Institute, Dr. Sjostrand holds a Bachelor degree in Economics from the Stockholm School of Business.

Hans Wigzell, M.D., Ph.D., is Professor and Chairman of the Department of Immunology at the Karolinska Institute, Stockholm, Sweden, one of the leading medical research institutes in Europe. He is a member of the Nobel Committee for the prize in medicine, of which he recently served as chairman. Professor Wigzell currently is a member of the editorial board of several international medical journals and has published more than 400 articles in the areas of tumor biology, immunology, cell biology and infectious diseases. Professor Wigzell is also the Chairman of the Company's Scientific Advisory Board.

Scientific Advisory Board

In August 1992, the Company established a Scientific Advisory Board, which currently consists of nine members. The Scientific Advisory Board discusses on a regular basis, and meets annually to evaluate the Company's research and development projects. Members of the Scientific Advisory Board receive $500 per meeting actually attended and are reimbursed for reasonable out-of-pocket expenses. In addition, each member of the Scientific Advisory Board, with the exception of Dr. Berglund, Professor Wigzell, Dr. Horsman and Dr. Chaplin, each of whom joined the

Scientific Advisory Board after its formation, has received warrants to purchase 5,000 shares of Common Stock, at an exercise price of $1.95 per share, expiring in May 1998, and options to purchase 2,500 shares of Common Stock, at an exercise price of $7.25 per share, expiring in December, 2003. Prior to establishment of the Scientific Advisory Board, certain of its members advised the Company on certain projects. Certain members of the Scientific Advisory Board also have other relationships with the Company, as described below.

Dr. Berglund, who joined the Scientific Advisory Board in December 1993, received options to purchase a total of 5,000 shares of Common Stock, exercisable at $7.25 per share, expiring in December 2003. Professor Wigzell, who joined the Scientific Advisory Board on August 10, 1994, received stock appreciation rights with respect to 30,000 shares of Common Stock, at a reference price of $7.63 per share, expiring in August 2004. These stock appreciation rights vest in three equal annual installments on each of August 1995, 1996, and 1997. In addition, Professor Wigzell receives cash compensation of $10,000 per annum. Dr. Horsman, who joined the Scientific Advisory Board in November 1994, received options to purchase 5,000 shares of Common Stock, exercisable at $5.50 per share. Dr. Chaplin, who joined the Scientific Advisory Board in May 1995, received options to purchase 30,000 shares of Common Stock, at an exercise price of $5.375 per share, expiring in May 2005. These options vest in three equal annual installments on each of May 30, 1996, 1997, and 1998. In addition, Dr. Chaplin receives cash compensation of $30,000 per annum.

The members of the Company's Scientific Advisory Board are:

Hans Wigzell, M.D., Ph.D., is Chairman of the Scientific Advisory Board. His biography is listed above under the subcaption "- Advisors to Board of Directors."

David J. Chaplin, Ph.D., is Head of the United Kingdom Cancer Research Campaigns Tumour Microcirculation Group based at the Gray Laboratory, the Mount Vernon Hospital, Middlesex, United Kingdom and an internal consultant to the Company (see "Business-Research and Development and Collaborative Arrangements"). The Gray Laboratory is one of the leading radiation biology research laboratories in the world. Dr. Chaplin has published more than 100 papers in the area of chemical radiosensitizers and tumor biology.

Goran Berglund, M.D., Ph.D., is Professor of Medicine, Malmo General Hospital, Vice Dean, Faculty of Medicine, Lund University, Sweden. Dr. Berglund has published numerous articles, most recently on the biological bank and biomarker program aspects of the Malmo Diet Study.

Michael Horsman, Ph.D., is Senior Scientist in the Danish Cancer Societies' Department of Clinical Oncology in Aarhus, Denmark. Dr. Horsman has published more than 100 papers on the chemical modification of radiation and heat damage in tumors.

Myron Jacobson, Ph.D., is Professor and Chairman of the Division of Medicinal Chemistry and Pharmaceuticals and a member of the Lucille Parker Markey Cancer Center of the University of Kentucky. Dr. Jacobson has published more than 100 papers in the area of biological responses to DNA damage. Dr. Jacobson acts also as a consultant to the Company regarding certain technical and clinical aspects of the Company's research and development program (see "Business--Research and Development and Collaborative Arrangements").

Dick Killander, M.D., Ph.D., , is Professor and Chairman of the Department of Oncology, University of Lund Hospital, Lund, Sweden. Dr. Killander serves on the board of the Swedish Cancer Foundation, and has published more than 100 articles in the areas of quantitative cytochemistry and

clinical oncology. Dr. Killander is the principal clinical investigator for the Company's clinical trial that is currently in progress (see "Business--Introduction").

Daniel G. Miller, M.D., is President of the Strang Cancer Prevention Center, New York, New York, and has held several posts at Memorial Sloan-Kettering Cancer Center and The New York Hospital-Cornell Medical Center in New York, New York. Dr. Miller has been a cancer consultant to the World Health Organization in Thailand and the Radiation Effects Research Foundation in Hiroshima, Japan. He is the founder, and served as the first President, of the American Society of Preventive Oncology.

Michael P. Osborne, M.D., is Director of Strang-Cornell Breast Center and is an Attending Surgeon in the Department of Surgery at The New York Hospital-Cornell Medical Center, both in New York, New York. Dr. Osborne has published more than 100 articles on breast cancer.

Mark E. Smulson, Ph.D., is Professor of Biochemistry and Molecular Biology, Georgetown University Medical Center, Washington, D.C., and heads that University's Lombardi Cancer Center's Program of ADP-Ribosylation and DNA Repair. Dr. Smulson has published approximately 100 papers and chapters on the molecular biology aspects of the ADPRT gene.

Executive Compensation

During the fiscal year-ended December 31, 1995, the aggregate renumeration paid to all officers and directors of the Company as a group (then six persons) was approximately $707,000.

Option Holdings as of August 30, 1996

The following table sets forth, as of August 30, 1996, the number of exercisable and unexercisable options held by each of the Company's executive officers.

Number of Unexercised Options/Warrants at August 30, 1996

Name	Exercisable	Unexercisable
Bjorn Nordenvall	165,000	165,000
Claus Moller	58,333	46,667
Ronald W. Pero	260,000	0
Bo Haglund	0	30,000
M. Andica Kunst	0	30,000

Certain Relationships and Related Transactions

IPC Nordic Consulting Agreement. In August 1995, the Company entered into a consulting agreement with IPC Nordic A/S, a company organized under the laws of Denmark ("IPC") of which Dr. Claus Moller, a director and the Chief Medical Officer of the Company, is the president and a principal

shareholder. Pursuant to the agreement, IPC and Dr. Moller provide services with respect to the Company's clinical trials and a possible future compassionate use program in consideration of a monthly consulting fee of Dkr.70,245 (approximately $11,970 based on an exchange rate of U.S.$0.1704 to one Danish Krone).

Omentum Consulting Agreement. In October 1995, the Company entered into a consulting agreement with B. Omentum Consulting AB, a company organized under the laws of Sweden ("Omentum") of which Dr. Bjorn Nordenvall, a director and the President and Chief Executive Officer of the Company, is the sole shareholder. Pursuant to the agreement, the Company pays Omentum an annual consulting fee of $50,000.

1996 Stock Incentive Plan

General. Certain directors, officers and employees of the Company and its subsidiary and consultants and advisors thereto may be granted options to purchase shares of Common Stock of the Company or stock appreciation rights ("SARs") under the 1996 Plan. The number of consultants, advisors, employees and other service providers eligible to receive awards under the 1996 Plan is not presently determinable.

A maximum of 1,000,000 shares of Common Stock may be made the subject of options and SARs granted under the 1996 Plan. No employee may be granted options or free-standing SARs with respect to more than 500,000 shares of Common Stock. That number of shares may be adjusted in the event of certain changes in the capitalization of the Company.

The 1996 Plan will be administered by a committee of at least two directors (the "Committee"), each of whom will be "disinterested" within the meaning of Rule 16b-3 promulgated under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and an "outside director" within the meaning of Section 162(m) of the Code. The Committee will have authority, subject to the terms of the 1996 Plan, to determine when and to whom to make grants under the plan, the number of shares to be covered by the grants, the types and terms of options and SARs granted, the exercise price of the shares of Common Stock covered by options and SARs and to prescribe, amend and rescind rules and regulations relating to the 1996 Plan. Options granted to non-employee directors are governed by the formula discussed below. Options granted under the 1996 Plan may not be transferred to another person except by will or the laws of descent and distribution.

Director Options. Directors who are not employees of the Company ("Nonemployee Directors") will be granted an option to purchase 55,000 shares of Common Stock on the first business day following the annual meeting of stockholders of the Company beginning with the 1996 Annual Meeting. Thereafter, on the first business day following each successive annual meeting, so long as shares remain available under the 1996 Plan, each Nonemployee Director who is first elected as a director at such meeting shall be granted options in respect of 55,000 shares. Each Nonemployee Director will receive options with respect to no more than 55,000 shares of Common Stock. The per share exercise price will be equal to the fair market value of a share of Common Stock on the date the option is granted. Options granted to Nonemployee Directors will be exercisable in five equal annual installments of 11,000 shares on each anniversary of the date of grant. Options granted to Nonemployee Directors will expire 10 years from the option grant date.

Employee Options. Under the terms of the 1996 Plan, "incentive stock options" ("ISOs") within the meaning of Section 422 of the Code, "nonqualified stock options" ("NQSOs") and SARs may be granted by the Committee to employees of the Company and any of its affiliates and to consultants and service providers to the Company or any present or future Affiliate Companies (as defined in the 1996 Plan) (each a "Participant"), except that ISOs may be granted only to employees of the Company and any of its subsidiaries. The per share purchase price (the "Option Price") under each Option granted to a Participant shall established by the Committee on the time the Option is granted. However, the per share Option Price of an ISO granted to a Participant shall not be less than 100% of the Fair Market Value of a share on the date the ISO is granted (110% in the case of an ISO granted to a Ten-Percent Stockholder). Participant Options will be exercised at such times and in such installments as determined by the Committee. The Committee may accelerate the exercisability of any Participant Option at any time. Each Option granted pursuant to the 1996 Plan shall be for such term as determined by the Committee, provided, however, that no Employee Option shall be exercisable after the expiration of ten years from its grant date (five years in the case of an ISO granted to a Ten-Percent Stockholder).

General Requirements. Options granted pursuant to the 1996 Plan generally may not be exercised more than three months after the option holder ceases to provide services to the Company or an affiliate, except that in the event of the death or permanent and total disability of the option holder, the option may be exercised by the holder (or the holder's estate, as the case may be), for a period of up to one year after the date of death or permanent and total disability. The agreements evidencing the grant of an option (other than an option to a Nonemployee Director) may, in the sole and absolute discretion of the Committee, set forth additional or different terms and conditions applicable to such option upon a termination or change in status of the employment or service of the optionee. Options terminate immediately if the option holder's service was terminated for cause.

The shares purchased upon the exercise of an option are to be paid for in cash (including cash that may be received from the Company at the time of exercise as additional compensation) or through the delivery of other shares of Common Stock with a value equal to the total Option Price or in a combination of cash and such shares. In addition, the option holder may have the Option Price paid by a broker or dealer and the shares issued upon exercise of the option delivered directly to the broker or dealer.

Stock Appreciation Rights. The Committee also may grant SARs either alone ("Free Standing Rights") or in conjunction with all or part of an option ("Related Rights"). Upon the exercise of an SAR a holder is entitled, without payment to the Company, to receive cash, shares of Common Stock or any combination thereof, as determined by the Committee, in an amount equal to the excess of the fair market value of one share of Common Stock over the exercise price per share specified in the related option (or in the case of a Free Standing Right, the price per share specified in such right), multiplied by the number of shares of Common Stock in respect of which the SAR is exercised.

Amendment or Termination. The Board of Directors of the Company has the power to terminate or amend the 1996 Plan at any time. If the Board of Directors does not take action to earlier terminate the 1996 Plan, it will terminate on March 11, 2006. Certain amendments may require the approval of the Company's stockholders, and no amendment may adversely affect options that have previously been granted.

PRINCIPAL STOCKHOLDERS

The following table sets forth the number of shares of Common Stock beneficially owned, as of September 16, 1996 and as adjusted to give effect to the Offering, by (i) each holder of more than 5% of the Common Stock, as reported the Company by such holder on reports on Schedule 13D or Schedule 13G under the Exchange Act, (ii) each of the Company's directors and executive officers and (iii) the directors and executive officers of the Company as a group. Unless otherwise noted, all shares are owned directly with sole voting and dispositive powers.

Name(1)	Beneficial Ownership(2)			
	No. of Shares		% of Total Before Offering	% of Total As Adjusted
Ronald W. Pero	690,000	(3)	8.73%	7.75%
Bjorn Nordenvall	380,000	(4)	4.86%	4.31%
Claus Moller	58,333		*	*
Michael Ionata	5,000	(5)	*	*
Marvin H. Caruthers	1,500	(6)	*	*
Bo Haglund	0		*	*
M. Andica Kunst	0		*	*
Richard A. Brown	864,900	(7)	10.66%	9.49%
Morgan Grenfell Asset Management	698,000		9.13%	8.07%
Invesco PLC	464,400		6.07%	5.37%
All directors and executive officers as a group (7 persons)	1,134,833		13.95%	12.42%

- ---

* Indicates less than one percent.

(1) Each person listed in the table is a director or executive officer of the Company, with an address at c/o OXiGENE, Inc., 110 E. 59th Street, New York, NY 10022, except for Richard A. Brown, whose address is 17 Prospect Hill Road, Box 1116, Stockbridge, MA 01262; Invesco PLC, which address is 11 Devonshire Square, London EC2M 4YR, England; and Morgan Grenfell Asset Management Limited, which address is 20 Finsbury Circus, London EC2M 1NB, England.

(2) Includes the following shares which are purchasable under options and warrants that are presently exercisable or exercisable within 60 days of the date of this table: Dr. Pero - 260,000 shares; Dr. Nordenvall - 165,000 shares; Dr. Moller - 58,333 shares; Mr. Ionata - 5,000 shares; and Mr. Brown 465,000 shares.

(3) Includes 70,588 shares held by a trust for the benefit of Dr. Pero's children, and 120,588 shares held by The Ronald Pero Charitable Remainder Unitrust, a trust of which Dr. Pero is the trustee.

(4) Includes 1,000 shares held by his spouse as to which Dr. Nordenvall disclaims beneficial ownership; 142,700 held by a corporation organized and the laws of Sweden of which Dr. Nordenvall is the sole stockholder; and 71,300 shares held through a capital insurance placed by Dr. Nordenvall.

(5) Options are held by Nordberg Capital Inc., a New York investment banking firm, of which Mr. Ionata is Director of Corporate Finance and the directors, officers and key employees of which own, collectively, 72,800 shares of OXiGENE Common Stock.

(6) Includes 1,000 shares held by spouse in trust for children, as to which Professor Caruthers disclaims beneficial ownership.

(7) Includes 20,000 shares held for the benefit of his minor child.

DESCRIPTION OF SECURITIES

Introduction

On August 26, 1993, OXiGENE completed an initial public offering of 1,605,000 units, each unit consisting of one share of common stock, par value $.01 per share ("Common Stock"), and one warrant ("Public Warrants") to purchase an additional share of Common Stock. The Common Stock and the Public Warrants are traded on the Nasdaq SmallCap System under the symbols "OXGN" and "OXGNW," respectively. See "Market Data."

Common Stock

The Company is authorized to issue 15,000,000 shares of Common Stock. At the 1996 Annual Meeting of Stockholders, the Company's stockholders approved an amendment to the Company's Amended and Restated Certificate of Incorporation, increasing the number of authorized shares of Common Stock from 15 million to 60 million shares. No amendment to the Company's Amended and Restated Certificate of Incorporation has been filed to date. On August 30, 1996, 7,645,508 shares of Common Stock were outstanding. The holders of Common Stock are entitled to one vote for each share held of record on all matters to be voted on by stockholders. There is no cumulative voting with respect to the election of directors. As a consequence, the holders of more than 50% of the shares voting for the election of directors can elect all the directors. The By-Laws provide that only a majority of the issued and outstanding shares of Common Stock need to be represented for a quorum, and to transact business at a stockholders' meeting. The holders of Common Stock are entitled to receive dividends when, as and if declared by the Board of Directors out of the funds legally available therefor. The Company has no present plans to pay dividends with respect to the shares of Common Stock. In the event of liquidation, dissolution or the winding up of the Company, the holders of Common Stock are entitled to share ratably in all assets remaining available for distribution after payment of liabilities and after provision has been made for each class of stock, if any, having preference over the Common Stock. Holders of shares of Common Stock, as such, have no conversion, preemptive or other subscription rights, and there are no redemption provisions applicable to the Common Stock. All the outstanding shares of Common Stock are, and the Shares offered hereby when issued against payment therefor, will be, validly authorized and issued, fully paid and nonassessable.

Public Warrants

The Public Warrants were issued pursuant to a Warrant Agreement between the Company and American Stock Transfer Company, as a warrant agent, and are in registered form. Currently, each of the Public Warrants entitles the registered holder thereof to purchase 1.07 shares of Common Stock, at a price of $12.35 per share (the "Exercise Price"), which Exercise Price shall be increased by $2.00 on August 26, 1997. Unless exercised, the Public Warrants will automatically expire on the close of business on August 26, 1998. On August 30, 1996, an aggregate of 1,193,241 Public Warrants remained outstanding.

The holders of the Public Warrants have certain anti-dilution protection upon the occurrence of certain events, including stock dividends, stock splits, mergers and reclassifications. The holders of the Public Warrants have no right to vote on matters submitted to the stockholders of the Company, have no right to receive dividends, and have none of the other rights conferred upon stockholders of the

Company. The holders of the Public Warrants are not entitled to share in the assets of the Company in the event of liquidation, dissolution or the winding up of the Company's affairs.

UNDERWRITING

Each of the underwriters named below (the "Underwriters"), for whom D. Carnegie AB is acting as representative (the "Representative"), has severally agreed, subject to the terms and conditions of the underwriting agreement, dated _____, 1996, between the Company and the Underwriters (the "Underwriting Agreement"), to purchase from the Company the aggregate number of Shares set forth opposite its name below:

Underwriter	Number of Shares
D. Carnegie AB.....	
Nordberg Capital Inc.	
Total.....	1,000,000

The Underwriting Agreement provides that the obligations of the Underwriters to purchase the Shares listed above are subject to certain conditions precedent, including the approval of certain legal matters by counsel. The Underwriting Agreement also provides that the Underwriters are committed to purchase all of the Shares if any are purchased.

Concurrently, and in connection with, this Offering, the Company is offering 1,000,000 Shares in the form of Swedish Depository Shares ("SDSs") for sale to the public in Sweden and in certain other countries outside the United States. ("Bank") will serve as Custodian for the SDSs pursuant to a Custody Agreement between the Bank, as Custodian, and the Company. The Shares will, upon receipt of payment for Shares by the Company, be delivered to the Bank to be held in custody pursuant to the Custody Agreement. In accordance with Swedish practice, following this Offering persons who own SDSs may trade in those SDSs in Sweden, as well as in any other markets in which trading in such SDSs is permitted, and may also exchange SDSs for Shares and trade in such Shares in Sweden, in a private transaction not transacted on the Stockholm Stock Exchange, and the United States. Further, following this Offering, persons who own shares of Common Stock of the Company will be able to exchange them for SDSs that can be traded in those markets in which such trading is permitted. As a result of, and subject to, the foregoing, a trading market for shares of Common Stock of the Company, as well as for SDSs, may arise in Sweden. A more complete description of the SDSs and the terms and conditions of the initial public offering and Custodian arrangements regarding them are contained in a Swedish Prospectus of which this Prospectus is a part.

The Underwriters have advised the Company that the Underwriters propose to offer the Shares in the form of SDSs directly to the public at the public offering price set forth on the cover page of this Prospectus, and to certain dealers at such price less a concession not in excess of $ per share. The Underwriters may allow, and such dealers may reallow, a concession not in excess of $ per share to certain other dealers. After the commencement of the public offering, the offering price and other selling terms may be changed by the Representative.

Mr. Michael Ionata, a director of the Company, is Director of Corporate Finance of Nordberg Capital Inc., one of the Underwriters.

LEGAL MATTERS

The validity of the Shares has been passed upon by Battle Fowler LLP, New York, New York, a limited liability partnership including professional corporations.

EXPERTS

The consolidated financial statements of the Company at December 31, 1995 and 1994, and for each of the three years in the period ended December 31, 1995, appearing in this Prospectus and Registration Statement have been audited by Ernst & Young LLP, independent auditors, as set forth in their report thereon appearing elsewhere herein, and are included in reliance upon such report given upon the authority of such firm as experts in accounting and auditing.

GLOSSARY OF SCIENTIFIC TERMS

ADPRT	Adenosine Diphosphate Ribosyl Transferase - an enzyme involved in the DNA repair process
Anti-emetic	A drug which controls nausea and vomiting
Apoptosis	A natural programmed cell death not involving cell replication
CD4 cell counts	A sub-set of white blood cells directly involved in the natural protection against diseases
CGLP standards	Current good laboratory practice standards required for regulatory affairs
Chemotheraphy	Drugs that control cancer growth
Cisplatin	A chemotherapeutic compound
Control group	A group of patients involved in a clinical trial who are receiving placebos
Cross-over study	A study in which each patient receives all treatments singly, but at different times of the study
Cytotoxic agent	Tumor-killing agent
DNA	Chemical building blocks of genetic material
Double-blind study	A study in which neither the investigators assessing the outcome of the trial nor the patients know whether the patient is receiving the drug being investigated or merely a placebo. The outcome can only be determined when the results are decoded
Enzyme	A protein that carries out a metabolic function by converting one substance to another
Genetic blueprint	The code that tells cells what to do and how to function
Genetic lesions	Damage to the DNA or in the genetic blueprint

i.m.	Intramuscular
Immune deficiencies	Suppression of the cells that fight disease within the body
IND	An "Investigational New Drug" application filed with the U.S. Food and Drug Administration that permits the administration of compounds to humans in clinical trials
In vivo-exposed spleen and cell	Spleen cells are exposed in the animal then taken out for testing
Isozyme	One of several forms of the same enzyme
i.v.	Intraveneous
Malignant cell	Cancer cell
Metabolic function	Living process of growth and reproduction
NDA	A "New Drug Application" filed with the U.S. Food and Drug Administration, which, if approved, allows a drug to be marketed in the U.S.
Necrosis	Cell death by decomposition after replication
N-substituted benzamide	Class of drugs believed by OXiGENE to sensitize radiation and chemotheraphy
Nucleotides	A class of nucleic acid compounds from which genes are constructed
Oxidative stress	Undesired natural metabolism of oxygen-derived molecules by the body that can induce DNA damage
Placebo	A non-active substance given to a control group of patients in a clinical trial to duplicate the treatment method, but without the administration of the active drug under investigation
Radiation	Physical energy that splits molecules and induces DNA damage

Sensitization	The process that renders a tumor more susceptible to damage by radiation or chemotherapy
Serum thiol level	The level of compounds in serum that react with oxidative stress

Appendix I

The following sets forth additional information regarding the Company's clinical trials. This information is qualified in its entirety and should be read in conjunction with the information contained elsewhere in this Prospectus.

Clinical Study - Sensamide(TM) in NSCLC, Phase I/II

This open label, historically controlled trial, assessing the safety of Sensamide(TM) when used in combination with radiotherapy, was conducted at the Department of Oncology, University Hospital in Lund, Sweden. A total of 23 with NSCLC, 21 male and 2 female, varying in age from 52 to 81 years, were enrolled in this study. All patients were treated with radiation and received Sensamide(TM) intravenously. Radiation was administered five days per week for six weeks. Eighteen patients completed the study as planned. Complete or partial remission, as defined by World Health Organization criteria, was achieved in 50 percent of the patients.

The majority of patients enrolled in this study experienced no unexpected side effects associated with the administration of Sensamide(TM). There was no evidence of increased radiation-associated toxicity to skin, lung, cardiac or esophageal tissues in the majority of patients. None of the patients had their treatment interrupted due to radiotherapy-associated toxicity.

Adverse events associated with Sensamide(TM) were mainly CNS-related (central nervous system-related) and were comparable to those resulting from anti-emetic metoclopramide therapy. Eighteen patients (78 percent) experienced sedation or tiredness and 11 patients (48 percent) experienced anxiety and restlessness. Depression, insomnia and other CNS-related reactions were experienced by two patients each. Akineton, a drug used to treat the side effects induced by Sensamide(TM), was administered to 44 percent of the patients to relieve those side effects. Five of the 23 enrolled patients dropped out of the study due to Sensamide(TM)-associated adverse CNS-effects. The occurrence of sedation or tiredness and the total occurrence of Sensamide(TM)- associated adverse CNS effects was significantly greater in patients receiving a total dose of metoclopramide greater than 2,000 mg, as compared to patients receiving less than 2,000 mg during the whole course of the therapy.

A preliminary assessment of the efficacy of Sensamide(TM) as adjunct therapy to radiation in patients with NSCLC is based on the results of this study. The assessment includes the determination of tumor response and survival. Of the 23 involved in the study, one could not be evaluated due to death prior to the first follow-up examination. Of the remaining patients, complete response was recorded in 9 percent of the patients, partial response in 41 percent, stable disease in 41 percent and progressive disease in 9 percent. The mean duration of tumor response in these patients was 10.8 +/- 8.5 months. The mean and median survival time of patients treated with Sensamide(TM) plus radiation was approximately 15.3 months and 12.8 months, respectively. This survival time is longer than that reported in the literature for patients with severe NSCLC who received radiation only. Eleven historical control patients with inoperable NSCLC treated in Lund had a mean and median survival of 7.0 and 5.0 months, respectively. Mean survival time correlated significantly with the total dose of Sensamide(TM) administered. Complete or partial responders who had a mean survival time of 22.1 +/- 3.9 months (mean + standard error) received an average total dose of 2,272 + 543 mg (mean + standard deviation) of Sensamide(TM). In contrast, non-responders who received an average total dose of 1,579 + 571 mg (mean +/- standard deviation) of Sensamide(TM) had a mean survival time of 12.6 +/- 2.4 months (mean + standard deviation).

400608.6

Clinical Study - Sensamide(TM) in NSCLC, Phase II/III

This study was initiated by OXiGENE in the middle of 1994 in Scandinavia and later expanded to include Germany and the United Kingdom (the "U.K."). The purpose of this Phase II/III multicenter, randomized, controlled trial is to assess the safety, tolerance and efficacy of Sensamide(TM) (2 mg/kg i.v., delivered one hour prior to radiation) as adjunct treatment to radiation as compared to radiation only in the treatment of 226 patients with NSCLC. Patients receive radiation five times per week and Sensamide(TM) three times per week for six and one half weeks. Currently, approximately 180 patients have been recruited. At the current recruitment rate, patient recruitment is expected to be completed by the end of 1996.

Clinical Study - Sensamide(TM) i.v., Neu-Sensamide(TM) i.m./i.v., Phase I

The primary objective of this randomized cross-over study, conducted at Guilford Clinical Pharmacology Unit in the U.K., was to assess the safety of single, radiosensitizing doses (2 mg/kg) of Neu-Sensamide(TM) when administered as an i.m. injection or as an i.v. infusion compared with an i.v. dose of Sensamide(TM) or an i.m. placebo injection. The secondary objective was to compare the pharmacokinetics of Neu-Sensamide(TM) when administered as a single i.m. injection or i.v. infusion with that of i.v. infused Sensamide(TM).

The difference between Neu-Sensamide(TM) and Sensamide(TM) is a changed formulation, resulting in two different conformational forms of metoclopramide. Thus Sensamide(TM) is acidic (pH of around 2.5-3.8) like any traditional metoclopramide suspension whereas Neu-Sensamide(TM) is phosphate buffered and neutralized with a pH of around 6.7.

Eleven healthy volunteers, varying in age from 53 to 63 years, completed the study. The results revealed a safety profile of Neu-Sensamide(TM) i.m. similar to that of Sensamide(TM) i.v. However, Sensamide(TM) i.v. impaired cognition to a larger extent than Neu-Sensamide(TM), both i.v. and i.m. In addition, adverse events were less frequent and of shorter duration with Neu-Sensamide(TM), both i.v. and i.m., than with Sensamide(TM) i.v. Bioavailability of Neu-Sensamide(TM) i.m. was comparable to that of Neu-Sensamide(TM) i v. and Sensamide(TM) i.v. Local tolerability of Neu-Sensamide(TM) i.m. was comparable to that of placebo i.m.

Nineteen healthy volunteers participated in this study. One was withdrawn due to non-compliance with the protocol, 7 volunteers dropped out due to adverse effects, and 11 volunteers completed the study. During the 53 treatment sequences of those patients that completed the study, a total of 93 adverse effects were reported; 37 after Sensamide(TM) i.v., 24 after Neu-Sensamide(TM) i.v., 25 after Neu-Sensamide(TM) i.m., and 7 after the placebo. No unexpected adverse effects associated with either Sensamide(TM) or Neu-Sensamide(TM) occurred throughout the study. Thus, adverse effects occurred significantly less frequently in volunteers receiving Neu-Sensamide(TM) than in those receiving Sensamide(TM).

No differences in pharmacokinetics could be detected in the study, apart from, as expected, in the peak plasma concentration between Neu- Sensamide(TM) i.m. and Sensamide(TM)/Neu- Sensamide(TM) i.v.

Clinical Study - Neu-Sensamide(TM) in NSCLC, Phase III

This Phase III study has been planned on the basis of the results of the Phase I study described above, and is based on the design of the ongoing, controlled Phase II/III with Sensamide(TM) in NSCLC.

400608.6

This randomized, multi-center, controlled Phase III study will assess the safety, tolerance and efficacy of Neu-Sensamide(TM) as a radiosensitizing agent compared to radiotherapy only for the treatment of NSCLC. Patients who satisfy the inclusion criteria and who are appropriate for treatment with 60 Gray radiation will be enrolled into the study. Patients will be randomized to receive either radiotherapy only or radiation plus Neu-Sensamide(TM) (2 mg/kg i.m.).

The study is expected to start in the fourth quarter of 1996 and will involve about 20 U.S. and European oncology centers. Patients will undergo a 45-day treatment period. Adverse effects, vital signs and laboratory values will be monitored periodically for safety evaluation. During the post-treatment follow-up period, patients will be followed for 1.5 years. The primary efficacy parameters will be duration of tumor response and survival.

Clinical Study - Neu-Sensamide(TM) in Glioblastomas, Phase I/II

This study will assess the safety and tolerability of Neu-Sensamide(TM) as a radiosensitizing agent in patients receiving a six-week treatment of 54 Gray of radiotherapy, following operative biopsy, subtotal or macroscopical total excision of their glioblastoma multiforme. The study is designed as a single-center, open-label, dose escalation study. The patients will be assigned in a consecutive manner to receive escalating doses of Neu-Sensamide(TM) from 2 to 8 mg/kg i.m. All patients will receive their study medication one hour prior to the administration of each fraction of radiotherapy. A total of up to 15 consecutive patients will be recruited. Patients will be treated in groups of three with increasing doses of Neu-Sensamide(TM). The post-treatment review of the patients will be conducted at weeks 4, 8, 12, 24, 36 and 48. Patient enrollment commenced in August 1996 and will continue into 1997.

The primary safety parameter will be the incidence of signs and symptoms of CNS toxicity, such as neurological reactions, psychological reactions, restlessness/insomnia, sedation and convulsions. Secondary parameters will include the incidence of other adverse effects and significant laboratory value changes during and after treatment. In addition, tumor response evaluations will be performed. If the results of the Oxi-104 study so warrant, OXiGENE intends to initiate a large controlled Phase III study in patients with glioblastomas.

Clinical Study - Oxi-104, Phase I

The Company currently anticipates commencing a Phase I clinical test of Oxi-104 after the filing of an IND with the U.S. Food and Drug Administration in the second quarter of 1997. Based on preliminary results, OXiGENE believes it can demonstrate that Oxi-104 alone can induce tumor growth-inhibiting and tumor-killing effects.

Non-GLP (non-good laboratory practices) toxicology studies have indicated the safety of Oxi-104 in doses five to ten times higher than the maximum doses needed for obtaining optimal anti-cancer effects. In vivo and in vitro animal studies have demonstrated that Oxi-104 can sensitize and induce a one to eight fold increase in the effect of established chemotherapeutic agents such as cisplatin, gemcitabine, bleomycin, ara-C and melphalan.

OXiGENE, Inc.
(A development stage company)

Index to Financial Statements

Annual Financial Statements:

Unaudited Interim Financial Statements:

Schedules for which provision is made in the applicable accounting regulation of the Securities and Exchange Commission are not required under the related instructions or are inapplicable and, therefore, have been omitted.

Report of Independent Auditors

The Board of Directors and Stockholders
OXiGENE, Inc.

We have audited the accompanying consolidated balance sheets of OXiGENE, Inc. (the "Company") (a development stage company) as of December 31, 1995 and 1994, and the related consolidated statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 1995. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with generally accepted auditing standards. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of OXiGENE, Inc. (a development stage company) at December 31, 1995 and 1994, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 1995 in conformity with generally accepted accounting principles.

ERNST & YOUNG LLP

New York, New York
February 27, 1996

OXiGENE, Inc.
(A development stage company)

Consolidated Balance Sheets

	December 31 1994	1995
Assets		
Current assets:		
Cash and cash equivalents	$ 1,193,999	$ 10,406,605
Securities available-for-sale (Note 2)	3,291,128	502,020
Prepaid expenses	207,967	50,180
Interest receivable	44,955	202,164
Other	-	19,132
Total current assets	4,738,049	11,180,101
Furniture, fixtures and equipment, at cost	33,598	62,087
Accumulated depreciation	10,296	24,537
	23,302	37,550
Deposits	9,600	9,600
Total assets	$ 4,770,951	$ 11,227,251
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses:		
Due to CATO Research, Ltd. (Note 6)	$ 122,109	$ 133,734
Accrued expenses	45,900	259,301
Accrued stock appreciation rights	-	223,095
Other payables	122,960	53,947
Total current liabilities	290,969	670,077
Commitments (Note 5)		
Stockholders' equity (Note 3):		
Common stock, $.01 par value:		
Authorized shares--		
10,000,000 shares at December 31, 1994		
15,000,000 shares at December 31, 1995		
Issued and outstanding shares--		
5,058,100 shares at December 31, 1994		
6,823,300 shares at December 31, 1995	50,581	68,233
Common stock subscribed	-	50
Additional paid-in capital	12,188,565	21,864,364
Deficit accumulated during the development stage	(7,682,039)	(11,399,874)
Foreign currency translation adjustment	-	24,894
Unrealized losses on securities available-for-sale	(77,125)	(493)
Total stockholders' equity	4,479,982	10,557,174
Total liabilities and stockholders' equity	$ 4,770,951	$ 11,227,251

See accompanying notes.

OXiGENE, Inc.
(A development stage company)

Consolidated Statements of Operations

	Year ended December 31			Period from February 22, 1988 (inception) through December 31,
	1993	1994	1995	1995
				(Unaudited)
Revenues				
Research income	$ -	$ -	$ -	$ 31,000
Interest income	50,897	265,440	420,949	747,241
	50,897	265,440	420,949	778,241
Operating expenses				
Research and development:				
CATO Research, Ltd. (Note 6)	468,083	608,337	739,994	2,465,223
Other	411,112	1,156,125	2,103,599	4,604,537
Total research and development	879,195	1,764,462	2,843,593	7,069,760
General and administrative	1,191,714	1,340,737	1,295,191	5,108,355
Total operating expenses	2,070,909	3,105,199	4,138,784	12,178,115
Net loss	$ (2,020,012)	$ (2,839,759)	$ (3,717,835)	$ (11,399,874)
Net loss per common share	$ (0.50)	$ (.56)	$ (.63)	
Weighted average number of common shares outstanding	4,026,456	5,037,278	5,876,295	

See accompanying notes.

OXiGENE, Inc.
(A development stage company)
Statements of Stockholders' Equity (Deficit)
(Note 2)

	Date	Common Stock, $.01 Par Value Shares	Common Stock, $.01 Par Value Amounts	Common Stock Subscribed Shares	Common Stock Subscribed Amount	Additional Paid-In Capital	Deficit Accumulated During the Development Stage
Issuance of common stock in exchange for transfer of patent application ownership to the Company by an officer/director recorded at no value, which reflects transferor's basis (unaudited)	May 1988	380,000	$3,800	-	$ -	$ (3,800)	$ -
Issuance of common stock at approximately $0.74 per share (unaudited)	June 1988	271,033	2,710	-	-	197,290	-
Issuance of common stock in exchange for the outstanding common stock of Bio-Screen Inc. (unaudited)	August 1988	100,000	1,000	-	-	(1,000)	-
Net loss for period from February 22, 1988 (inception) through December 31, 1988 (unaudited)		-	-	-	-	-	(185,962)
Balance at December 31, 1988 (unaudited)		751,033	7,510	-	-	192,490	(185,962)
Issuance of common stock at approximately $0.74 per share (unaudited)	January 1989	271,033	2,710	-	-	197,290	-
Net loss for 1989 (unaudited)		-	-	-	-	-	(179,119)
Balance at December 31, 1989 (unaudited)		1,022,066	10,220	-	-	389,780	(365,081)
Issuance of common stock at approximately $0.74 per share	March 1990 to December 1990	257,487	2,575	-	-	187,425	-
Common stock subscribed	December 1990	-	-	13,547	10,000	-	-
Net loss for 1990		-	-	-	-	-	(326,648)
Balance at December 31, 1990		1,279,553	12,795	13,547	10,000	577,205	(691,729)
Issuance of common stock at approximately $0.74 per share	January 1991	13,547	136	(13,547)	(10,000)	9,864	-
Issuance of common stock at $0.71 per share	February 1991	330,000	3,300	-	-	230,033	-
Issuance of common stock at approximately $1.50 per share	August 1991	100,000	1,000	-	-	149,000	-
Issuance of common stock at $1.95 per share	December 1991	220,000	2,200	-	-	426,800	-
Net loss for 1991		-	-	-	-	-	(501,872)
Balance at December 31, 1991		1,943,100	19,431	-	-	1,392,902	(1,193,601)
Issuance of common stock at $1.95 per share, net of issuance costs of approximately $121,000	December 1992	985,000	9,850	-	-	1,789,866	-
Net loss for 1992		-	-	-	-	-	(1,628,667)
Balance at December 31, 1992		2,928,100	29,281	-	-	3,182,768	(2,822,268)

	Date	Foreign Currency Translation Adjustment	Stock Subscription and Notes Receivable	Unrealized Losses on Securities Available for Sale	Total Stockholders' Equity (Deficit)
Issuance of common stock in exchange for transfer of patent application ownership to the Company by an officer/director recorded at no value, which reflects transferor's basis (unaudited)	May 1988	$ -	$ -	$ -	$ -
Issuance of common stock at approximately $0.74 per share (unaudited)	June 1988	-	-	-	200,000
Issuance of common stock in exchange for the outstanding common stock of Bio-Screen Inc. (unaudited)	August 1988	-	-	-	-
Net loss for period from February 22, 1988 (inception) through December 31, 1988 (unaudited)		-	-	-	(185,962)
Balance at December 31, 1988 (unaudited)		-	-	-	14,038
Issuance of common stock at approximately $0.74 per share (unaudited)	January 1989	-	-	-	200,000

Net loss for 1989 (unaudited)		-	-	-	(179,119)
Balance at December 31, 1989 (unaudited)		-	-	-	34,919
Issuance of common stock at approximately $0.74 per share	March 1990 to December 1990	-	-	-	190,000
Common stock subscribed	December 1990	-	(10,000)	-	-
Net loss for 1990		-	-	-	(326,648)
Balance at December 31, 1990		-	(10,000)	-	(101,729)
Issuance of common stock at approximately $0.74 per share	January 1991	-	10,000	-	10,000
Issuance of common stock at $0.71 per share	February 1991	-	-	-	233,333
Issuance of common stock at approximately $1.50 per share	August 1991	-	-	-	150,000
Issuance of common stock at $1.95 per share	December 1991	-	-	-	429,000
Net loss for 1991		-	-	-	(501,872)
Balance at December 31, 1991		-	-	-	218,732
Issuance of common stock at $1.95 per share, net of issuance costs of approximately $121,000	December 1992	-	(360,750)	-	1,438,966
Net loss for 1992		-	-	-	(1,628,667)
Balance at December 31, 1992		-	(360,750)	-	29,031

OXiGENE, Inc.
(A development stage company)
Statements of Stockholders' Equity (Deficit) (continued)
(Note 2)

	Date	Common Stock, $.01 Par Value Shares	Common Stock, $.01 Par Value Amounts	Common Stock Subscribed Shares	Common Stock Subscribed Amount	Additional Paid-In Capital	Deficit Accumulated During the Development Stage
Issuance of common stock at $1.95 per share, net of issuance costs of approximately $136,500	January 1993 to February 1993	445,000	$4,450	-	$ -	$ 726,800	$ -
Repayment of notes receivable	January 1993	-	-	-	-	-	-
Issuance of warrants and options as compensation to certain directors to purchase 180,000 and 10,000 shares of common stock, respectively, at $1.95 per share	May 1993	-	-	-	-	427,500	-
Issuance of common stock at $6.00 per share, net of issuance costs of approximately $1,836,000	September 1993	1,500,000	15,000	-	-	7,149,247	-
Issuance of common stock at $6.00 per share, net of issuance costs of approximately $82,000	October 1993	105,000	1,050	-	-	547,050	-
Net loss for 1993		-	-	-	-	-	(2,020,012)
Balance at December 31, 1993		4,978,100	49,781	-	-	12,033,365	(4,842,280)
Issuance of common stock at $1.95 per share	April 1994	80,000	800	-	-	155,200	-
Net loss for 1994		-	-	-	-	-	(2,839,759)
Unrealized losses on securities available-for-sale		-	-	-	-	-	-
Balance at December 31, 1994		5,058,100	50,581	-	-	12,188,565	(7,682,039)
Issuance of options as compensation to consultants to purchase 165,000 shares of common stock at $6.00 per share	June 1995	-	-	-	-	20,625	-
Issuance of common stock at $6.00 per share, net of issuance costs of approximately $524,000	July 1995	1,666,700	16,667	-	-	9,460,009	-
Issuance of common stock at $1.50 per share (12,500) and $1.95 per share (86,000)	July 1995 to December 1995	98,500	985	-	-	185,465	-
Subscriptions for 5,000 shares of common stock at $1.95 per share	December 1995	-	-	5,000	50	9,700	-
Foreign currency translation adjustment for 1995		-	-	-	-	-	-
Net loss for 1995		-	-	-	-	-	(3,717,835)
Unrealized gain on securities available-for-sale		-	-	-	-	-	-
Balance at December 31, 1995		6,823,300	$68,233	5,000	$ 50	$21,864,364	$(11,399,874)

	Date	Foreign Currency Translation Adjustment	Stock Subscription and Notes Receivable	Unrealized Losses on Securities Available For Sale	Total Stockholders' Equity (Deficit)
Issuance of common stock at $1.95 per share, net of issuance costs of approximately $136,500	January 1993 to February 1993	$ -	$ -	$ -	$ 731,250
Repayment of notes receivable	January 1993	-	360,750	-	360,750
Issuance of warrants and options as compensation to certain directors to purchase 180,000 and 10,000 shares of common stock, respectively, at $1.95 per share	May 1993	-	-	-	427,500
Issuance of common stock at $6.00 per share, net of issuance costs of approximately $1,836,000	September 1993	-	-	-	7,164,247
Issuance of common stock at $6.00 per share, net of issuance costs of approximately $82,000	October 1993	-	-	-	548,100
Net loss for 1993		-	-	-	(2,020,012)
Balance at December 31, 1993		-	-	-	7,240,866
Issuance of common stock at $1.95 per share	April 1994	-	-	-	156,000

Net loss for 1994		-	-	-	(2,839,759)
Unrealized losses on securities available-for-sale		-	-	(77,125)	(77,125)
Balance at December 31, 1994		-	-	(77,125)	4,479,982
Issuance of options as compensation to consultants to purchase 165,000 shares of common stock at $6.00 per share	June 1995	-	-	-	20,625
Issuance of common stock at $6.00 per share, net of issuance costs of approximately $524,000	July 1995	-	-	-	9,476,676
Issuance of common stock at $1.50 per share (12,500) and $1.95 per share (86,000)	July 1995 to December 1995	-	-	-	186,450
Subscriptions for 5,000 shares of common stock at $1.95 per share	December 1995	-	-	-	9,750
Foreign currency translation adjustment for 1995		24,894	-	-	24,894
Net loss for 1995		-	-	-	(3,717,835)
Unrealized gain on securities available-for-sale		-	-	76,632	76,632
Balance at December 31, 1995		$ 24,894	$ -	$ (493)	$10,557,174

See accompanying notes.

OXiGENE, Inc.
(A development stage company)

Consolidated Statements of Cash Flows

	Year ended December 31			Period from February 22, 1988 (inception) through December 31
	1993	1994	1995	1995
				(Unaudited)
Operating activities				
Net loss	$ (2,020,012)	$ (2,839,759)	$ (3,717,835)	$(11,399,874)
Adjustments to reconcile net loss to net cash used in operating activities:				
Loss on securities available-for-sale	-	-	9,460	9,460
Depreciation	3,808	5,044	13,773	24,069
Compensation related to issuance of warrants, options and stock appreciation rights	427,500	-	243,720	671,220
Changes in operating assets and liabilities:				
Prepaid expenses and other current assets	(294)	(252,628)	(14,740)	(267,662)
Accounts payable and accrued expenses	146,657	(19,001)	146,248	437,217
Net cash used in operating activities	(1,442,341)	(3,106,344)	(3,319,374)	(10,525,570)
Financing activities				
Proceeds from investor	-	-	-	100,000
Repayment to investor	-	-	-	(100,000)
Proceeds from issuance and subscription of common stock, net	8,804,347	156,000	9,672,876	21,484,522
Net cash provided by financing activities	8,804,347	156,000	9,672,876	21,484,522
Investing activities				
Purchases of securities available-for-sale	-	(3,368,253)	-	(3,368,253)
Proceeds from sale of securities available-for-sale			2,856,280	2,856,280
Deposits	-	-	-	(9,600)
Purchase of furniture, fixtures and equipment	(9,713)	(4,345)	(26,922)	(60,520)
Net cash (used in) provided by investing activities	(9,713)	(3,372,598)	2,829,358	(582,093)
Effect of exchange rate on changes in cash	-	-	29,746	29,746
Net (decrease) increase in cash and cash equivalents	7,352,293	(6,322,942)	9,212,606	10,406,605
Cash and cash equivalents at beginning of period	164,648	7,516,941	1,193,999	-

	Year ended December 31			Period from February 22, 1988 (inception) through December 31
	1993	1994	1995	1995
				(Unaudited)
Cash and cash equivalents at end of period	$ 7,516,941	$ 1,193,999	$ 10,406,605	$10,406,605

See accompanying notes.

OXiGENE, Inc.
(A development stage company)

Notes to Consolidated Financial Statements

December 31, 1995

1. Description of Business and Significant Accounting Policies

Description of Business

OXiGENE, Inc. (the "Company") is a development stage pharmaceutical company. The Company was originally incorporated as Oxi-Gene, Inc. in the State of New York on February 22, 1988 and subsequently recapitalized and incorporated in the State of Delaware in December 1992.

The Company is in the research phase of its operations. Because operations to-date have consisted of research activities only, no substantial income has been generated to-date and the losses sustained result principally from outlays for research and administrative expenses. The Company will need to obtain additional funds from outside sources to fund operating expenses, pursue regulatory approvals and build production, sales and marketing capabilities, as necessary.

Principles of Consolidation

In December 1994, the Company established a wholly-owned subsidiary in Sweden, OXiGENE (Europe) AB to manage and control the Company's research and development work, and monitor European clinical trials. The accounts of the subsidiary have been consolidated from the time the subsidiary commenced operations in January 1995. All material intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reported period. Actual results could differ from those estimates.

1. Description of Business and Significant Accounting Policies (continued)

Depreciation

Furniture, fixtures and equipment are recorded at cost. Depreciation is provided using the straight-line method over the estimated useful lives of the assets which is principally seven years.

Cash and Cash Equivalents

The Company considers all highly liquid financial instruments with a maturity of three months or less when purchased to be cash equivalents.

Substantially all cash and cash equivalents are deposited in one financial institution at December 31, 1995. Substantially all cash and cash equivalents were deposited in another financial institution at December 31, 1994.

Foreign Currency Translation

Assets and liabilities of the subsidiary are translated at year-end rates and income and expenses are translated at average exchange rates prevailing during the year. Translation adjustments arising from differences in exchange rates from period to period are included in the accumulated foreign currency translation adjustments account in stockholders' equity.

Investments

The Company accounts for marketable securities in accordance with the provisions of Statement of Financial Accounting Standards No. 115, "Accounting for Certain Investments in Debt and Equity Securities."

Management determines the appropriate classification of debt securities at the time of purchase and reevaluates such designation as of each balance sheet date. Debt securities are classified as held-to-maturity when the Company has the positive intent and ability to hold the securities to maturity.

1. Description of Business and Significant Accounting Policies (continued)

Investments (continued)

Debt securities not classified as held-to-maturity are classified as available-for-sale. Available-for-sale securities are stated at fair value, with the unrealized gains and losses reported in a separate component of shareholders' equity.

The amortized cost of debt securities classified as held-to-maturity or available-for-sale is adjusted for amortization or premiums and accretion of discounts to maturity. Such amortization is included in interest income from investments. Realized gains and losses, and declines in value judged to be other-than-temporary are included in net securities gains (losses). The cost of securities sold is based on the specific identification method.

Patent and Patent Applications

The Company has filed applications for patents in connection with technologies being developed. The patent applications and any patents issued as a result of these applications are important to the protection of the Company's technologies that may result from its research and development efforts. The pharmaceutical industry is highly competitive and patents may be challenged from time to time. The Company intends to vigorously defend its issued patents and may therefore incur significant costs in the defense of the patents and related technologies. Costs associated with the patent and patent applications are expensed as incurred.

Income Taxes

The Company accounts for income taxes based upon the provisions of Statement of Financial Accounting Standards No. 109, "Accounting for Income Taxes" ("SFAS 109"). Under SFAS 109, the liability method is used for accounting for income taxes, and deferred tax assets and liabilities are determined based on differences between financial reporting and tax bases of assets and liabilities.

1. Description of Business and Significant Accounting Policies (continued)

Share Information

All outstanding share amounts included in the accompanying financial statements have been adjusted to reflect the 10,000 for 1 stock split disclosed in Note 3.

Unaudited Information

Information pertaining to the period from February 22, 1988 (inception) through December 31, 1989 is unaudited.

Net Loss Per Share

Net loss per share is based upon net loss divided by weighted average number of shares of common stock outstanding during the respective periods, retroactively adjusted to reflect the stock split. The weighted average number of common shares outstanding has been computed in accordance with Staff Accounting Bulletin 83 ("SAB 83") of the Securities and Exchange Commission. SAB 83 requires that shares of common stock and warrants, issued within a one-year period prior to the initial filing of a registration statement relating to an initial public offering at amounts substantially below the public offering price, be considered outstanding for all periods presented in the Company's Registration Statement. During the one-year period preceding the effectiveness of the Company's registration statement in August 1993, the Company issued 1,290,000 shares of common stock at $1.95 per share and warrants to purchase 387,500 shares of common stock exercisable at $1.95 per share. Accordingly, for purposes of calculating loss per share amounts, such shares have been considered outstanding for all periods presented, and such warrants have been considered outstanding through June 30, 1993. For purposes of calculating net loss per share, the initial offering price was assumed to be $6 per share (see Note 3). All other options and warrants were antidilutive and, accordingly, excluded from the calculation of weighted average shares.

1. Description of Business and Significant Accounting Policies (continued)

Stock-Based Compensation

In October 1995, the Financial Accounting Standards Board (FASB) issued Statement of Financial Accounting Standards No. 123, "Accounting for Stock-Based Compensation" ("SFAS 123"). SFAS 123 is effective for fiscal years beginning after December 31, 1995 and prescribes accounting and reporting standards for all stock-based compensation plans, including employee stock options, restricted stock, employee stock purchase plans and stock appreciation rights. SFAS 123 requires compensation expense to be recorded (i) using the new fair value method or (ii) using existing accounting rules prescribed by Accounting Principles Board Opinion No. 25, "Accounting for Stock Issued to Employees" ("APB 25") and related interpretations with pro forma disclosure of what net income and earnings per share would have been had the Company adopted the new fair value method. The Company presently accounts for its stock based compensation plans in accordance with the provisions of APB 25 and has not determined if it intends to change to the fair value method prescribed in SFAS 123.

2. Investments

The following is a summary of securities available-for-sale:

	Securities Available-for-Sale		
	Cost	Gross Unrealized Losses	Estimated Fair Value
December 31, 1994			
U.S. Government securities:			
U.S Treasury Notes	$ 1,342,644	$ 31,546	$ 1,311,098
Student Loan Marketing Association	1,001,256	22,256	979,000
	2,343,900	53,802	2,290,098
U.S. corporate debt securities:			
American Express Credit Corporation	522,893	14,938	507,955
Ford Motor Credit Company	501,460	8,385	493,075
	1,024,353	23,323	1,001,030
	$ 3,368,253	$ 77,125	$ 3,291,128

2. Investments (continued)

December 31, 1995			
U.S. corporate debt securities:			
American Express Credit Corporation	$ 502,513	$ 493	$ 502,020
	$ 502,513	$ 493	$ 502,020

The amortized cost and estimated fair value of debt securities at December 31, 1995, by contractual maturity are shown below.

	Cost	Fair Value
Available-for-Sale		
Due in one year or less	$ 502,513	$ 502,020

3. Stockholders' Equity

Options and Warrants

The following is a summary of the Company's stock option and warrant activity.

	Nonqualified Stock Options	Stock Incentive Options	Stock Appreciation Rights	Stock Warrants
Balance at December 31, 1992	12,500	240,000	-	506,000
Granted during 1993	197,500	125,000	22,500	2,056,500
Balance at December 31, 1993	210,000	365,000	22,500	2,562,500
Granted during 1994	-	-	52,500	-
Exercised during 1994	-	(80,000)	-	-
Canceled during 1994	-	(160,000)	-	-
Balance at December 31, 1994	210,000	125,000	75,000	2,562,500
Granted during 1995	669,000	-	2,000	-
Exercised during 1995	(12,500)	-	-	(86,000)
Canceled during 1995	(2,000)	-	-	-
Balance at December 31, 1995	864,500	125,000	77,000	2,476,500

3. Stockholders' Equity (continued)

Nonqualified Stock Options

In August 1991, the Company's Board of Directors granted options to a former officer of the Company to purchase 12,500 shares of the Company's common stock at $1.50 per share exercisable at any time prior to August 7, 2001. During 1995, such options to purchase 12,500 shares of the Company's common stock were exercised.

In December 1993, under the Amended Plan, as defined below, the Company's Board of Directors granted options to certain directors of the Company and other individuals to purchase 197,500 shares of the Company's common stock at $7.25 per share. Such options vested at various dates over a period of one year from the date of grant and are exercisable at any time prior to December 13, 2003.

In November 1994, under the Amended Plan, the Company's Board of Directors granted options, subsequently approved by stockholders in May 1995, to certain director's of the Company and other individuals to purchase 252,000 shares of the Company's common stock at market value ($5.59 per share). Such options vest at various dates over a period of 28 months from the date of grant.

In 1995, under the Amended Plan, the Company's Board of Directors granted to certain directors of the Company and other individuals options to purchase 417,000 shares of the Company's common stock at exercise prices ranging from $5.375 per share to $7.00 per share. Options to purchase 252,000 shares were granted at exercise prices equal to the market value of the shares on date of grant. The remaining 165,000 shares are exercisable at $6.00 per share. Because the market price of the Company's shares amounted to $6.125 per share on the date these options were granted, the Company recorded a charge for financial reporting purposes of approximately $20,625.

3. Stockholders' Equity (continued)

Stock Incentive Options

During 1992, the Board of Directors implemented an Stock Incentive Option Plan (the "Plan"). The Plan provided for the grant of options to purchase up to 250,000 shares of common stock to any officer, director and employee of the Company upon the terms and conditions (including price, exercise date and number of shares) determined by the Board of Directors or a committee selected by the Board of Directors to administer the Plan.

In April 1992, under the Plan, the Company's Board of Directors granted stock options to an officer of the Company for the purchase of 240,000 shares of the Company's common stock at $1.95 per share. Such options vest at 80,000 per year for a three-year period. During 1994, vested options to purchase 80,000 shares of the Company's common stock were exercised. The remaining nonvested options to purchase 160,000 shares of the Company's common stock were cancelled upon the termination of the officer's services in 1994.

On May 15, 1993, under the Plan, the Board of Directors granted options as compensation to certain directors of the Company, to purchase 10,000 shares of common stock at $1.95 per share, exercisable at any time for a period of five years.

During May 1993, the Company amended and restated its Stock Incentive Plan (the "Amended Plan"). Under the Amended Plan, the Company has reserved for issuance an additional 416,900 shares of Common Stock. The Amended Plan provides for the issuance of stock appreciation rights.

Under the Amended Plan, the exercise price determined by the Board of Directors or committee must be at least 100% of the fair market value of the Company's common stock as of the date of the grant. Upon termination of employment, any granted option, vested or unvested, shall, to the extent not previously exercised, terminate except under certain conditions as outlined in the Amended Plan. The options granted under the Amended Plan are generally exercisable at specific dates over a ten-year period.

3. Stockholders' Equity (continued)

In December 1993, under the Amended Plan, the Company's Board of Directors granted stock options to a certain director of the Company to purchase 115,000 shares of common stock at $8.00 per share. Such options vested in equal installments on December 14, 1993 and 1994.

Stock Appreciation Rights

Under the Amended Plan, the Company's Board of Directors granted stock appreciation rights to 22,500 shares of common stock at an exercise price of $7.25 per share and stock appreciation rights to another 22,500 shares at an exercise price of $5.875 per share to an employee, certain consultants and clinical investigators on December 14, 1993 and April 4, 1994, respectively. Such stock appreciation rights vested in equal installments on December 14, 1994 and 1995.

In September 1994, under the Amended Plan, a member of the scientific advisory board received stock appreciation rights to 30,000 shares of common stock at $7.63 per share. Such stock appreciation rights vest in equal installments in September 1994, 1995 and 1996.

In July 1995, under the Amended Plan, a consultant received stock appreciation rights to 2,000 shares of common stock at $5.38 per share. Such stock appreciation rights vest in equal installments on July 13, 1995 and July 13, 1996.

On December 31, 1995, the market value per share of common stock ($10.25) exceeded the exercise price of the stock appreciation rights and, accordingly, the Company recorded a charge for financial reporting purposes of approximately $223,000.

Stock Warrants

In November 1991, and January and June 1992, the Board of Directors granted warrants to directors of the Company to purchase 50,000, 370,000 and 50,000 shares, respectively, of the Company's common stock at $1.95 per share exercisable at any time for a period of five years. In connection with the sale of stock during December 1992, the placement agents were granted warrants to purchase 36,000 shares of the Company's stock at $1.95

3. Stockholders' Equity (continued)

Stock Warrants (continued)

per share exercisable for a five-year period. During 1995, warrants to purchase 86,000 shares of the Company's common stock were exercised. In addition, as of December 31, 1995, $9,750 was subscribed to exercise warrants to purchase 5,000 shares of common stock. Such shares were issued in 1996.

From January 1, 1993 through February 26, 1993, the Company sold 445,000 shares of common stock to investors for approximately $868,000 ($1.95 per share). In connection with this issuance of stock, the placement agents were granted warrants for the purchase of 66,500 shares of the Company's common stock at $1.95 per share exercisable for a five-year period.

In January 1993, the Board of Directors granted warrants to the Company's scientific advisory board to purchase 45,000 shares of the Company's common stock at $1.95 per share exercisable at any time for a period of five years.

On May 15, 1993, the Board of Directors granted warrants as compensation to certain directors of the Company, to purchase 180,000 shares of common stock at $1.95 per share exercisable at any time for a period of five years. The Company has recorded a charge of $427,500 for financial reporting purposes, representing the estimated value of such options and warrants granted on May 15, 1993.

During 1993, the Company completed an initial public offering of 1,500,000 units at $6.00 per unit and an over-allotment issuance of 105,000 units at $6.00 per unit. Each unit consists of one share of the Company's common stock and one warrant. Each warrant is exercisable for one share of the Company's common stock at a price of $7 per share during the first year of exercisability. Thereafter, the exercise price shall increase each year by $2.00 ($11 at December 31, 1995). On January 26, 1996, the exercise price of these warrants were reduced to $10.35 per share and the number of shares purchasable upon exercise of each warrant was increased to 1.07 (warrants to purchase 1,717,350 shares at $10.35 per share). In connection with this offering, the Company sold to the Underwriters, for nominal consideration, 150,000 Warrants (the "Underwriters'

3. Stockholders' Equity (continued)

Warrants"). The Underwriters' Warrants are initially exercisable at a price of $9.90 per Unit for a period of four years, commencing August 26, 1994. The shares of common stock and warrants issuable upon the exercise of the Underwriters' Warrants are identical to those included in the Units offered hereby except that the Warrants contained in the Underwriters' Warrants are initially exercisable to purchase one share of Common Stock at $11.55.

On December 14, 1993, the Board of Directors granted warrants to certain individuals of the Company to purchase 10,000 shares of common stock at $7.25 per share. Such warrants vested immediately.

Private Placement

In July 1995, the Company completed a private placement of 1,666,700 common shares at $6.00 per share, resulting in net proceeds (after deducting issuance costs) of approximately $9.5 million.

Common Stock Reserved for Issuance

As of December 31, 1995, the Company has reserved approximately 3,845,000 shares of its common stock for issuance in connection with stock options and warrants.

Recapitalization

During December 1992, in connection with the recapitalization (see Note 1), the Company changed its authorized common stock from 1,000 shares at $1.00 par value to 5,000,000 shares at $.01 par value. In addition, the Company declared a 10,000 for 1 stock split on the then issued and outstanding common shares.

In April 1993, the Company changed its authorized common stock from 5,000,000 shares at $.01 par value to 10,000,000 shares at $.01 par value.

In May 1995, the Company changed its authorized common stock from 10,000,000 shares at $.01 par value to 15,000,000 shares at $.01 par value.

3. Stockholders' Equity (continued)

Merger

During February 1991, the Company issued 100,000 shares of its common stock to an officer/director and a director for all the outstanding common stock of Bio-Screen, Inc. The balance sheet and the cumulative results of operations of Bio-Screen, Inc. were not material to the Company and, consequently, the statements of operations of the Company have not been restated. The issuance of the 100,000 shares, which have been recorded at par value, has been reflected as of August 1988, the date of inception of Bio-Screen, Inc. (see Note 5 "Commitments").

4. Income Taxes

Effective January 1, 1992, the Company changed its method of accounting for income taxes from the deferred method to the liability method required by Statement No. 109, "Accounting for Income Taxes" (see Note 1 "Significant Accounting Policies"). As permitted under the new rules, prior years' financial statements have not been restated. There was no cumulative effect on the Company's financial statements as a result of adopting Statement No. 109.

At December 31, 1995, the Company had net operating loss carryforwards of approximately $10,672,000 for U. S. and foreign income tax purposes, $8,838,000 expiring for U.S. purposes through 2010. For financial statement reporting purposes, a valuation allowance has been recognized to offset entirely the deferred tax assets related to the Company's net operating loss carryforwards and the temporary difference related to compensatory stock options and warrants.

Components of the Company's deferred tax asset at December 31, 1994 and 1995 are as follows:

	1994	1995
Net operating loss carryforwards	$ 2,880,000	$ 3,957,000
Compensatory stock options and warrants	171,000	268,000
Total deferred tax asset	3,051,000	4,225,000
Valuation allowance	(3,051,000)	(4,225,000)
Net deferred tax asset	$ -	$ -

4. Income Taxes (continued)

The change in valuation allowance amounted to approximately $802,000 and $1,120,000, respectively, for the years ended December 31, 1993 and 1994.

Changes in stock ownership (see Note 3) may result in a limitation on the annual utilization of net operating loss carryforwards.

5. Commitments and Contingencies

The Company subleases its office space at its facilities in New York . During 1995, the Company entered into a new lease for office space in Lund, Sweden. Rent expense for years ended December 31, 1993, 1994 and 1995 was approximately $53,000, $58,000 and $50,000, respectively.

The minimum annual rent commitments for the above leases are as follows:

1996	$ 55,400
1997	14,400
1998	1,200
	$ 71,000

In connection with the merger with Bio-Screen, Inc. (see Note 3), the Company obtained a license agreement to patent rights to a certain product. The agreement requires the Company to pay royalties, as defined, based on revenues received by the Company in respect to the specified product. The license expires in October 2011. The product has not yet been commercially developed.

From time to time the Company may be a party to litigation arising out of the normal course of its business. The Company is and will continue to vigorously defend the actions and claims against it. In the opinion of management, these claims are either without merit or, based in part on opinions from legal counsel, will not have a material adverse effect on the Company's financial position.

6. Related Party Transaction

In September 1991, the Company entered into an agreement with CATO Research, Ltd. ("CATO"), a North Carolina corporation, which is majority-owned by Dr. Cato, a member of the Company's Scientific Advisory Board, pursuant to which CATO performs preclinical and clinical planning, development and regulatory services in connection with the Company's efforts to obtain FDA approval for its technology. CATO is compensated by the Company on an hourly basis for services actually rendered. For the years ended December 31, 1993, 1994 and 1995, the Company incurred costs under this agreement totaling $468,083, $608,337 and $739,994, respectively.

7. Foreign Operations

Summary financial information for assets, liabilities at December 31, 1995 and expenses for the year ended December 31, 1995 for OXiGENE (Europe) AB are as follows:

Assets	$ 240,000
Liabilities	178,000
Expenses	1,853,000

Foreign exchange gains for the year ended December 31, 1995 were not significant.

OXiGENE, Inc.
(A development stage company)
Consolidated Balance Sheets
(All amounts in thousands of dollars, except share data)
(Unaudited)

	June 30, 1996
Assets	
Current assets:	
Cash and cash equivalents	$ 10,710
Securities available-for-sale	--
Prepaid expenses	80
Interest receivable	77
Other	21
Total current assets	10,888
Furniture, fixtures and equipment at cost	73
Accumulated depreciation	(31)
	42
Deposits	10
Total assets	$ 10,940
Liabilities and stockholders' equity:	
Current liabilities:	
Accounts payable and accrued expenses:	
Due to Cato Research, Ltd.	$ 75
Other payables	748
Total current liabilities	823
Stockholders' equity:	
Common stock $0.01 par value:	
Authorized shares - 15,000,000 shares	
Issued and outstanding	
7,271,282 at June 30, 1996	72
Additional paid-in capital	24,853
Common stock subscribed	98
Subscription receivable	(98)
Deficit accumulated during the development stage	(14,811)
Foreign currency translation adjustment	3
Total stockholders' equity	10,117
Total liabilities and stockholders' equity	$ 10,940

See accompanying notes.

OXiGENE, Inc.
(A development stage company)
Consolidated Statements of Operations
(All amounts in thousands of dollars, except share data)
(Unaudited)

	Six Months Ended		Period from February 22, 1988 (inception) through
	June 30, 1995	June 30, 1996	June 30, 1996
Revenue			
Research Income	$ -	$ -	$ 31
Interest income	82	254	1,001
Operating expenses:			
Research and development:			
Cato Research, Ltd.	282	388	2,853
Other	991	1,968	6,572
Total research and development	1,273	2,356	9,425
General and administrative	646	1,309	6,418
Total operating expenses	1,919	3,665	15,843
Net loss	$ (1,837)	$ (3,411)	$ (14,811)
Net loss per common share	$ (0.36)	$ (.49)	
Weighted average number of common shares outstanding	5,058	6,971	

See accompanying notes.

OXiGENE, Inc.
(A development stage company)
Consolidated Statements of Cash Flows
(All amounts in thousands of dollars)
(Unaudited)

	Six Months Ended		Period from February 22, 1988 (inception) through
	June 30, 1995	June 30, 1996	June 30, 1996
Operating activities			
Net loss	$ (1,837)	$ (3,411)	$ (14,811)
Adjustment to reconcile net loss to net cash used in operating activities:			
Depreciation	4	6	30
Amortization of debt securities	9	--	9
Compensation related to issuance of warrants options and stock appreciation rights	--	1,008	1,679
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	138	93	(175)
Accounts payable and accrued expenses	(52)	375	813
Net cash used in operating activities	(1,738)	(1,929)	(12,455)
Financing activities			
Proceeds from issuance of common stock, net	--	1,710	23,195
Other capital contributions	--	53	53
Net cash provided by financing activities	--	1,763	23,248
Investing activities			
Proceeds from sale of securities available-for-sale	848	502	3,358
Purchase of securities available for sale	--	--	(3,368)
Deposits	--	--	(10)
Purchase of furniture, fixture and equipment`	(18)	(11)	(71)
Net cash used in investing activities	830	491	(91)
Effect of exchange rate on changes in cash	--	(22)	8
Net increase (decrease) in cash and cash equivalents	(908)	303	10,710
Cash and cash equivalents at beginning of period	1,194	10,407	--
Cash and cash equivalents at end of period	$ 286	$ 10,710	$ 10,710

See accompanying notes.

OXiGENE, Inc.
(A development stage company)

Notes to Consolidated Financial Statements
June 30, 1996

Note l. Significant Accounting Policies

Basis of Presentation

The accompanying unaudited condensed financial statements have been prepared in accordance with generally accepted accounting principles for interim financial information and Article 10 of Regulation S-X. Accordingly, they do not include all of the information and footnotes required by generally accepted accounting principles for complete financial statements. In the opinion of management, all adjustments (consisting of normal recurring accruals) considered necessary for a fair presentation have been included. Operating results for the six-month period ended June 30, 1996 are not necessarily indicative of the results that may be expected for the year ending December 31, 1996. For further information, refer to the consolidated financial statements and footnotes thereto for the year ended December 31, 1995.

Cash and Cash Equivalents

The Company considers all highly liquid financial instruments with a maturity of three months or less when purchased to be cash equivalents.

Net Loss Per Share

Net loss per share is based upon the Company's aggregate net loss divided by the weighted average number of shares of common stock outstanding during the respective periods. All options and warrants were antidilutive and, accordingly, excluded from the calculation of weighted average shares.

Note 2. Principles of Consolidation

At the end of 1994, the Company established a wholly-owned operating subsidiary in Sweden, OXiGENE (Europe) AB. This subsidiary manages and controls the Company's research and development work, and monitors the European clinical trials. The consolidated financial statements include the accounts of the Company and OXiGENE (Europe) AB, effective January 1, 1995.

Intercompany balances and transactions have been eliminated.

Note 3. Stockholders' Equity

During the six months ended June 30, 1996, the company issued 447,982 shares of common stock upon exercise of previously granted options resulting in proceeds of approximately $1,710,000.

During the six months ended June 30, 1996, the Company recorded a charge for financial reporting purposes of approximately $1,008,000 because the market value of the Company's common stock ($25.50 at June 30, 1996) exceeded the exercise prices of stock appreciation rights issued by the Company. Because stock appreciation rights are satisfied, upon exercise, only by the distribution of shares of common stock of the Company, the charge was credited to additional paid-in capital. In addition, stock appreciation rights accrued as a liability as of December 31, 1995 amounting to approximately $223,000, which will not be paid in cash, was credited to additional paid-in capital during the six months ended June 30, 1996.

- ---------------------------

No dealer, salesman or any other person is authorized to give any information or to make any representations other than those contained or incorporated by reference in this Prospectus, and if given or made, such information or representations should not be relied upon as having been authorized. This Prospectus does not constitute an offer to sell, or a solicitation of an offer to buy the Shares, by anyone in any jurisdiction in which such offer to sell or solicitation is not authorized, or in which the person making such offer is not qualified to do so or to any person to whom it is unlawful to make such offer or solicitation. Neither the delivery of the Prospectus nor any distribution of shares pursuant to this Prospectus shall, under any circumstances, create any implication that there has been no change in the information set forth or incorporated by reference herein or in the affairs of the Company since the date of this Prospectus.

- --------------------------

PAGE

PART II

Item 14. Other Expenses of Issuance and Distribution.

The fees and expenses payable by the Company in connection with the issuance and distribution of the Shares being registered are estimated as follows:

	Amount
SEC Filing Fee	$ 9,914
Nasdaq Listing Fee	25,000
Legal Fees and Expenses*	135,000
Accounting Fees*	25,000
Printing and Translation Expenses*	52,780
Miscellaneous	2,306
Total	$250,000

* Indicates estimate

Item 15. Indemnification of Directors and Officers.

The Company is a Delaware corporation. Reference is made to Section 145 of the Delaware General Corporation Law (the "DGCL"), which provides that a corporation may indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed legal action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of such corporation), by reason of the fact that such person is or was an officer, director, employee or agent of such corporation, or is or was serving at the request of such corporation as an officer, director, employee or agent of another corporation, partnership, joint venture, trust or other enterprise. The indemnity may include expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by such person in connection with such action, suit or proceeding, provided such officer, director, employee or agent acted in good faith and in a manner reasonably believed by such person to be in or not opposed to the corporation's best interests and, for criminal proceedings, such person had no reasonable cause to believe that his conduct was unlawful. A Delaware corporation may indemnify officers and directors in an action by or in the right of the corporation under the same conditions, except that no indemnification is permitted in respect of any claim, issue or matter without judicial approval if the officer or director is adjudged to be liable to the corporation. Where an officer or director is successful on the merits or otherwise in the defense of any action referred to above, the corporation must indemnify such officer or director against the expenses (including attorneys' fees) that such officer or director actually and reasonably incurred.

Reference is also made to Section 102(b)(7) of the DGCL, which enables a corporation in its certificate of incorporation to eliminate or limit the personal liability of a director for monetary damages

for violations of the director's fiduciary duty, except (i) for any breach of the director's duty of loyalty to the corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) pursuant to Section 174 of the DGCL (providing for liability of directors for unlawful payment of dividends or unlawful stock purchases or redemptions) or (iv) for any transaction from which a director derived an improper personal benefit.

Article IX, Section 3 of the Company By-laws provides as follows:

"SECTION 3. Indemnification. The Corporation shall, to the fullest extent permitted by the General Corporation Law of the State of Delaware, indemnify members of the Board and may, if authorized by the Board, indemnify its officers, employees and agents and any and all persons whom it shall have power to indemnify against any and all expenses, liabilities or other matters."

ARTICLE NINTH of the Company's Restated Certificate of Incorporation provides as follows:

"To the fullest extent permitted by the General Corporation Law of the State of Delaware, no director of the Corporation shall be personally liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director, except for liability (i) for any breach of the director's duty of loyalty to the Corporation or its stockholders, (ii) for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the General Corporation Law of the State of Delaware, or (iv) for any transaction from which the director derived an improper personal benefit. Any repeal or modification of this Article Ninth by the stockholders of the Corporation shall not adversely affect any right or protection of a director of the Corporation existing at the time of such repeal or modification with respect to acts or omissions occurring prior to such repeal or modification."

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers or persons controlling the Company pursuant to the foregoing provisions, the Company has been informed that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Following the 1996 Annual Meeting of Stockholders, the Company entered into indemnification agreements with each of its directors and executive officers.

Item 16. Exhibits.

5*	Legal Opinion of Battle Fowler LLP
10.1	Form of Indemnification Agreement between the Company and its directors, executive officers and key employees
23.1	Consent of Ernst & Young LLP, New York, New York
23.2*	Consent of Battle Fowler LLP (included in Exhibit 5)
24.1	Power of Attorney (included herein on the signature page)
99.1	U.S. Patent Number 5,204,241, issued April 20, 1994, registered to Ronald W. Pero, regarding glutathione-s-transferase Mu as a measure of drug resistance
99.2	U.S. Patent Number 5,340,565, issued August 23, 1994, registered to Ronald W. Pero, regarding tumor or cancer cell killing therapy and agents useful therefor
99.3	U.S. Patent Number 5,482,833, issued January 9, 1996, registered to Ronald W. Pero and Daniel G. Miller, regarding a test to determine the predisposition or susceptibility to DNA-associated diseases
99.4	International Application Published under the Patent Cooperation Treaty (PCT) Number WO96/14565, published May 17, 1996, registered to Ronald W. Pero, regarding a method of testing immune competency

* To be filed by amendment

Item 17. Undertakings

The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the Prospectus any facts or events arising after the effective date of this registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in this registration statement;

(iii) To include any material information with respect to the plan of distribution not previously disclosed in this registration statement or any material change to such information in this registration statement;

Provided, however, that paragraphs (1)(i) and (1)(ii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in periodic reports filed by the Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in this registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof; and

(3) To remove from registration by means of a post-effective amendment any of the securities which remain unsold at the termination of the offering.

The undersigned Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to section 13(a) or section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in this Registration Statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the Registrant pursuant to the provisions described above in Item 15, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question of whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

The undersigned Registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act of 1933 shall be deemed to be part of this registration statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized in the City of New York, State of New York, on September 23, 1996.

OXiGENE, INC.

By: /s/ Bjorn Nordenvall

Bjorn Nordenvall
President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Bjorn Nordenvall and Bo Haglund, and each of them, his true and lawful attorney-in-fact and agent, each acting alone, with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign any or all amendments to this Registration Statement, including post effective amendments, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents full power and authority to do and perform each and every act and thing requisite and necessary to be done, as fully to all intents and purposes as he might or could do in person, and hereby ratifies and confirms all his said attorney-in-fact and agents, each acting alone, or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Act of 1933, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Bjorn Nordenvall Bjorn Nordenvall	President, Chief Executive Officer and Chairman of the Board of Directors (Principal Executive Officer)	September 23, 1996
/s/ Bo Haglund Bo Haglund	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	September 23, 1996
/s/ Michael Ionata Michael Ionata	Director	September 26, 1996
/s/ Marvin H. Caruthers Marvin H. Caruthers	Director	September 26, 1996

/s/ Claus Moller Claus Moller	Chief Medical Officer and Director	September 26, 1996
/s/ Ronald Pero Ronald Pero	Chief Scientific Officer and Director	September 24, 1996

EXHIBIT INDEX

Exhibit Number	Description	Sequential Page Number
5*	Legal Opinion of Battle Fowler LLP	
10.1	Form of Indemnification Agreement between the Company and its directors, executive officers and key employee	
23.1	Consent of Ernst & Young LLP, New York, New York	
23.2*	Consent of Battle Fowler LLP	
24.1	Power of Attorney	
99.1	U.S. Patent Number 5,204,241, issued April 20, 1994, registered to Ronald W. Pero, regarding glutathione-s-transferase Mu as a measure of drug resistance	
99.2	U.S. Patent Number 5,340,565, issued August 23, 1994, registered to Ronald W. Pero, regarding tumor or cancer cell killing therapy and agents useful therefor	
99.3	U.S. Patent Number 5,482,833, issued January 9, 1996, registered to Ronald W. Pero and Daniel G. Miller, regarding a test to determine the predisposition or susceptibility to DNA-associated diseases	
99.4	International Application Published under the Patent Cooperation Treaty (PCT) Number WO96/14565, published May 17, 1996, registered to Ronald W. Pero, regarding a method of testing immune competency	

* To be filed by amendment.

INDEMNIFICATION AGREEMENT

THIS AGREEMENT, dated as of the ____ day of _____, 199_, is made by and between OXiGENE, Inc., a Delaware corporation having its principal place of business in the State of New York (the "Company") and _____ (the "Indemnitee"), a resident of _____.

WHEREAS, it is essential to the Company to retain and attract the most capable persons available as officers, directors and key employees; and

WHEREAS, Indemnitee is currently serving as _____ (the "Position"); and

WHEREAS, both the Company and Indemnitee recognize the increased risk of litigation and other claims being asserted against directors and officers of publicly-traded and other corporations, as a result of which competent and experienced persons have become more reluctant to serve in such positions, and as a result of which creative management and decision making has been deterred; and

WHEREAS, the provision of indemnification will assist the Company in attracting and retaining the most skilled and competent officers and directors; and

WHEREAS, in recognition of Indemnitee's need for substantial protection against personal liability in order to allow Indemnitee to continue to provide service to the Company in an effective manner, the Company wishes to provide in this Agreement for the indemnification of the Indemnitee and for the advancing of expenses to Indemnitee, in each case to the full extent permitted by law and as set forth in this Agreement.

NOW THEREFORE, in consideration of the premises and the covenants contained herein, the Company and Indemnitee agree as follows:

1. Agreement to Serve. Indemnitee will continue to serve faithfully and to the best of his ability in the Position, at the will of the Company or pursuant to the terms of any separate agreement which may exist, so long as he is duly elected or appointed and qualified or until such time as he tenders his resignation in writing.

2. Right to Indemnification. In the event Indemnitee was or is made a party or was or is threatened to be made a party to or was or is involved or called as a witness in any action, suit, proceeding or alternative dispute resolution mechanism, or any hearing, inquiry or investigation that Indemnitee in good faith believes may lead to the institution of such action, suit, proceeding or alternative dispute resolution mechanism, whether civil, criminal, administrative or investigative, and any appeal therefrom (hereinafter, collectively a "Proceeding"), by reason of the fact that he was, is or had agreed to become a director, officer, employee, agent, fiduciary or Delegate (as defined herein) of the Company, Indemnitee shall be indemnified and held harmless by the Company to the fullest extent permitted under the Delaware General Corporation Law (the "DGCL"), as the same now exists or may hereafter be amended (but, in the case of any such amendment, only to the extent that such amendment permits the Company to provide

broader indemnification rights than the DGCL permitted the Company to provide prior to such amendment) against all expenses (including reasonable attorneys' fees and all other costs, expenses, liabilities, obligations and disbursements in connection with investigating, prosecuting, defending, preparing to prosecute and defend, or being a witness or other participant in any Proceeding), liabilities and losses (including, but not limited to, judgements; fines; liabilities under ERISA for damages, excise taxes or penalties; damages, fines or penalties arising out of violation of any law related to the protection of the public health, welfare or the environment; and amounts paid or to be paid in settlement) incurred or suffered by such person in connection with any Proceeding (collectively, "Expenses"); provided, that except as provided in Section 6 hereof, the Company shall indemnify any such person seeking indemnity in connection with a Proceeding (or part thereof) initiated by such person only if such Proceeding (or part thereof) was authorized by the Board of Directors of the Company.

For purposes of this Agreement, a "Delegate" is any person serving at the request of the Company as a director, officer, trustee fiduciary, partner, employee or agent of an entity or enterprise other than the Company (including, but not limited to, service with respect to employee benefit plans and trusts).

3. Expenses. Expenses incurred by Indemnitee in defending or otherwise being involved in a Proceeding shall be paid by the Company in advance of the final disposition of such Proceeding, including any appeal therefrom, upon receipt of an undertaking (the "Undertaking") by or on behalf of Indemnitee to repay such amount if it shall ultimately be determined that he is not entitled to be indemnified by the Company; provided, that in connection with a Proceeding (or part thereof) initiated by Indemnitee, except as provided in Section 6 hereof, the Company shall pay such Expenses in advance of the final disposition only if such Proceeding (or part thereof) was authorized by the Board of Directors of the Company. The Undertaking shall provide that if Indemnitee has commenced Proceedings in a court of competent jurisdiction to secure a determination that he should be indemnified by the Company, he shall not be obligated to repay the Company during the pendency of such Proceeding.

4. Mandatory Payment of Expenses. Notwithstanding any other provision of this Agreement, to the extent that Indemnitee has been successful on the merits or otherwise, including, without limitation, the dismissal of an action without prejudice, in defense or any Proceeding or in the defense of any claim, issue or matter therein, Indemnitee shall be indemnified against all Expenses incurred by Indemnitee in connection therewith.

5. Notice. Indemnitee shall, as a condition precedent to Indemnitee's right to be indemnified under this Agreement, give the Company notice in writing as soon as practicable of any Proceeding for which indemnification will or could be sought under this Agreement.

6. Protection of Rights. If a claim under Section 2 or any agreement ("Other Agreement") providing indemnification to Indemnitee is not promptly paid in full by the Company after a written claim has been received by the Company or if Expenses pursuant to Section 3 or an Other Agreement have not been promptly advanced after a

written request for such advancement accompanied by the Undertaking has been received by the Company, the claimant may at any time thereafter bring suit against the Company to recover the unpaid amount of the claim or the advancement of Expenses. If successful, in whole or in part, in such suit Indemnitee shall also be entitled to be paid the reasonable expense thereof. It shall be a defense to any such action (other than an action brought to enforce a claim for Expenses incurred in defending any Proceeding in advance of its final disposition where the required Undertaking has been tendered to the Company) that Indemnitee has not met the standards of conduct which make it permissible under the DGCL for the Company to indemnify Indemnitee for the amount claimed, but the burden of proving such defense shall be on the Company. Neither the failure of the Company (including its Board of Directors, independent legal counsel, or its stockholders) to have made a determination that indemnification of Indemnitee is proper in the circumstances because he has met the applicable standard of conduct required under the DGCL, nor the actual determination by the Company (including its Board of Directors, independent legal counsel, or its stockholders) that Indemnitee had not met such applicable standard of conduct, shall be a defense to the action or create a presumption that Indemnitee had not met the applicable standard of conduct.

If a Change of Control has occurred, Indemnitee upon making a claim under Section 2 or seeking to avoid repayment to the Company pursuant to an Undertaking under Section 3 shall have (i) the right, but not the obligation, to have a determination made by independent legal counsel as to whether indemnification of the claimant is proper because he or she has met the applicable standard of conduct required under the DGCL; and (ii) shall have the right to select as independent legal counsel for such purpose any law firm as designated (or within a category designated) for such purpose in a resolution adopted by the Board of Directors of the Company prior to the Change of Control and in full force and effect immediately prior to the Change of Control. If a determination has been made in accordance with the preceding sentence, no determination inconsistent therewith by other legal counsel, by the Board of Directors, or by stockholders shall be of any force or effect, provided however, that Indemnitee shall maintain all rights granted hereby to bring an action as specified in the preceding paragraph.

A "Change of Control" shall be deemed to have occurred if (i) individuals who as of June 15, 1996 constitute the Board of Directors of the Company (the "Incumbent Directors") cease for any reason to constitute at least a majority of the Board of Directors of the Company, or (ii) there is a merger, consolidation or reorganization ("Merger") of the Company in which the Company is not the surviving entity (the "Survivor") and at any time following such Merger, Incumbent Directors do not constitute a majority of the Board of Directors of the Survivor; provided that any individual who becomes a director after June 14, 1996 whose election, or nomination for election by the Company's stockholders was approved by a vote or written consent of at least two-thirds of the directors then comprising the Incumbent Directors shall be deemed to be an Incumbent Director, but excluding, for this purpose, any such individual whose initial assumption of office is in connection with an actual or threatened election contest (as such term is used in Rule 14a-11 under the Securities Exchange Act of 1934, as amended) relating to the election of the directors of the Company.

7. No Presumption. For purposes of this Agreement, the termination of any Proceeding, by judgement, order, settlement (whether with or without court approval) or conviction, or upon a plea of nolo contendere or its equivalent, shall not create a presumption that Indemnitee did not meet any particular standard of conduct or have any particular belief or that a court has determined that indemnification or contribution is not permitted by applicable law.

8. Non-Exclusivity of Rights. The rights conferred on Indemnitee by this Agreement shall not be exclusive of any other right which Indemnitee may have or hereafter acquire under any statute, provision of the Company's Restated Certificate of Incorporation or By-Laws, other agreement, vote of stockholders or directors or otherwise.

9. Selection of Counsel. In the event the Company shall be obligated hereunder to pay the Expenses of any Proceeding, the Company shall be entitled to assume the defense of such Proceeding with counsel approved by Indemnitee, which approval shall not be unreasonably withheld, upon the delivery to Indemnitee of written notice of its election so to do. After delivery of such notice, approval of such counsel by Indemnitee and the retention of such counsel by the Company, the Company will not be liable to Indemnitee under this Agreement for any fees of counsel subsequently incurred by Indemnitee with respect to the same Proceeding; provided that, (i) Indemnitee shall have the right to employ Indemnitee's counsel in any such Proceeding at Indemnitee's expense and (ii) if (A) the employment of counsel by Indemnitee has been previously authorized by the Company, (B) Indemnitee shall have reasonably concluded that there is a conflict of interest between the Company and Indemnitee in the conduct of any such defense, or (C) the Company shall not continue to retain such counsel to defend such Proceeding, then the fees and expenses of Indemnitee's counsel shall be at the expense of the Company. The Company shall have the right to conduct such defense as it sees fit in its sole discretion, including the right to settle any claim against Indemnitee at the Company's expense without the consent of the Indemnitee.

10. Subrogation. In the event of any payment under this Agreement to Indemnitee, the Company shall be subrogated to the extent of such payment to all of the rights of recovery of Indemnitee, who shall execute all papers required and shall do everything that may be necessary to secure such rights, including execution of such documents as are necessary to enable the Company to bring suit to enforce such rights.

11. Exceptions. Any other provision herein to the contrary notwithstanding, the Company shall not be obligated pursuant to the terms of this Agreement:

(a) Excluded Action or Omissions. To indemnify Indemnitee for Expenses resulting from acts, omissions or transactions for which Indemnitee is prohibited from receiving indemnification under applicable law; and

(b) Claims under Section 16(b). To indemnify Indemnitee for expenses and the payment of profits arising from the purchase and sale by Indemnitee of securities in violation of Section 16(b) of the Securities Exchange Act of 1934, as amended, or any similar successor statute.

12. Amended; Waiver. No provision of this Agreement may be amended or modified except with the consent in writing of Indemnitee and the Company, nor may any provision of this Agreement be waived except in writing by the party granting such waiver. A waiver of any provision hereof shall not be deemed a waiver of any other provision hereof. Failure of either of the parties hereto to insist upon strict compliance with any provision hereof shall not be deemed to be a waiver of such provision or any other provision hereof.

13. No Duplication of Payments. The Company shall not be liable under this Agreement to make any payment in connection with any Proceeding to the extent Indemnitee has otherwise actually received payment under any insurance policy, statute, provision of the Company's Restated Certificate of Incorporation or By-Laws, other agreement, vote of stockholders or directors or otherwise of the amounts otherwise indemnifiable.

14. Partial Indemnification. If Indemnitee is entitled under any provision of this Agreement to indemnification by the Company for some or a portion of Expenses incurred in connection with any Proceeding, but not, however, for all of the total amount thereof, the Company shall nevertheless indemnify Indemnitee for the portion of such Expenses to which Indemnitee is entitled.

15. Binding Effect. This Agreement shall be binding upon and inure to the benefit of and be enforceable by the parties hereto and their respective successors and assigns (including, without limitation, any successor by purchase, merger, consolidation, reorganization or otherwise to all of substantially all of the business and/or assets of the Company) and their spouses, heirs, and personal and legal representatives.

16. Term. The provisions of this Agreement shall be applicable to all Proceedings, regardless of when commenced and regardless of whether relating to events, acts or omissions occurring before, on or after the date on which this Agreement becomes effective. This Agreement shall continue in effect regardless of whether Indemnitee continues to serve in the Position; provided, however, that notwithstanding any other provision hereof, the Company shall have no obligations hereunder with respect to liability, losses and Expenses of any Proceeding to the extent that such liability, losses and Expenses relate to conduct of the Indemnitee which occurs after Indemnitee no longer holds the Position nor a position of a corporate officer or director of the Company.

17. Severability. If this Agreement or any portion hereof shall be invalidated or held to be unenforceable, such invalidity or unenforceability shall not affect the other provisions hereof, and this Agreement shall be deemed to be modified to the minimum extent necessary to avoid such invalidity or unenforceability, and as so modified this Agreement and the remaining provisions hereof shall remain valid and enforceable in accordance with their terms to the fullest extent permitted by law.

18. Notice. All notices and other communications hereunder shall be in writing and delivered by hand or by first class registered or certified mail, return receipt requested, postage prepaid, addressed as follows:

If to the Indemnitee:

_____
_____
_____
_____

If to the Company:

OXiGENE, Inc.
110 East 59th Street
New York, NY 10022
Attention: President

or to such other address as either party shall have furnished to the other in writing in accordance herewith. Notice and communications shall be effective when actually received by the addressee.

19. Governing Law. This Agreement shall be governed by and construed and enforced in accordance with the laws of the state of Delaware, without regard to the principles thereof respecting conflicts of law.

20. Captions. The captions of this Agreement are not part of the provisions hereof and shall have no force or effect.

21. Counterparts. This Agreement may be executed in multiple counterparts, each of which shall be deemed to be an original but all of which together will constitute one and the same instrument originals.

IN WITNESS WHEREOF, Indemnitee and the Company, pursuant to the authorization of its Board of Directors, execute this Agreement on the date stated below.

OXiGENE, Inc.

By:_____
Title:
Date:

INDEMNITEE

_____
Name:
Date:

Consent of Independent Auditors

We consent to the reference to our firm under the captions "Selected Financial Information" and "Experts" and to the use of our report dated February 27, 1996, in the Registration Statement (Form S-3) and related Prospectus of OXiGENE, Inc. for the registration of 1,150,000 shares of its common stock.

ERNST & YOUNG LLP

New York, New York
September 25, 1996

407477.1

[GRAPHIC]
US005204241A

United States Patent Patent Number: 5,204,241

Pero Date of Patent: Apr. 20, 1993

GLUTATHIONE-S-TRANSFERASE MU AS A MEASURE OF DRUG RESISTANCE

Inventor: Ronald W. Pero, New York, N.Y.

Assignee: Oxi-Gene Inc., New York, N.Y.

Appl. No.: 601,266

Filed: Oct. 22, 1990

Int. Cl. C12Q 1/48; C12N 9/00
U.S. Cl. 435/15; 435/183
Field of Search 435/15, 183

References Cited

PUBLICATIONS

Leyland-Jones B.R. Antineoplastic Drug Sensitivity ... Chem. Abst. 114: 94779h Mar. 18, 1991.
Warholm M. Purification of a New GST Mu ... Biochem & Biophys Rsch Com 98 2: 512-519 Jan. 30, 1981.
Yusa K. Comparison of GST Activity Between ... Chem Abstracts, vol. 109, #13 109:104335y 1988.
Singh S. V. GST and Glutathione Peroxidases ... Chem. Abstracts 112:327t Jan. 1, 1990.
Morrow C.S. GST and Drug Resistance ... Chem. Abst. 112: 171572y May 7, 1990.
Begleiter A. Activity of Quinone Alkylating ... Chem. Abst. 113:70708n Aug. 27, 1990.
Seidegard, Janeric, Characterization of Soluble GST Activity ... Biochem. Pharm. 33 19: 3053-3058 1984.
Seidegard J. Hereditary Differences in the Expression ... Proc. Natl. Acad. Sci. USA 85:7293-7297 1988.
Peters W.H.M. Immunodetection with a Monoclonal Antibody ... Biochem. Pharm. 39 3:591-597 Jan. 1, 1990.

Johnston et al, J. Nat. Can. Inst., vol. 82, No. 9: 776-779 (1990).
Seidegard et al, Carcinogenesis, vol. 6, No. 8: 1211-1216 (1985).
Seidegard et al, J. Biochem. 246: 783-785 (1987).

Primary Examiner--John W. Rollins
Assistant Examiner--Ralph Gitomer
Attorney, Agent, or Firm--Cooper & Dunham

ABSTRACT

It has been discovered that by determining or measuring a person's glutathione-s-transferase (GST) mu activity one can determine or measure the individual's resistance to drugs, particularly to chemotherapeutic drugs. Approximately 50% of the human population exhibit substantially no GST mu activity, with the remaining 50% showing GST mu activity. This remaining 50% of the population accordingly, when treated with drugs, such as a chemotherapeutic drug for cancer therapy, show less effective response to the drug therapy than the other 50% of the population which have substantially no GST mu activity, since GST mu tends to deactivate drugs. Accordingly, a person having GST mu activity would exhibit drug resistance and would not benefit as much by or be as good a candidate for cancer chemotherapy as a person who has no GST mu activity.

13 Claims, 1 Drawing Sheet

406057.1

[GRAPHIC]

406057.1

GLUTATHIONE-S-TRANSFERASE MU AS A MEASURE OF DRUG RESISTANCE

BACKGROUND OF THE INVENTION

Glutathione-s-transferases (GSTs) are a group of multi-functional proteins which play an important role in the biotransformation of many different biologically active compounds, including agents which damage DNA, such as chemotherapeutic drugs, see Mannervik, B., Adv. Enzymol. Relat. Areas Mol. Biol. 57: 357-417 (1985). Indeed, it is known that GSTs are usually associated with the detoxification by conjugation of genotoxic and cytotoxic xenobiotic electrophiles derived from drugs, carcinogens and environmental pollutants, see Glutathione transferases; H. Sies and B. Ketterer (eds.), Glutathione Conjugation. Academic Press, New York, pp. 74-135 (1988).

On the basis of physical and immunological properties and substrate specificities and protein structure, the human GSTs have been divided into three distinct classes, named alpha, mu and pi, see Mannervik B., et al, Proc. Natl. Acad. Sci. U.S.A. 82: 7202-7206 (1985).

It is an object of this invention to employ glutathione-s-transferase activity as a measure of drug resistance.

How this and other objects of this invention are achieved will become apparent in the light of the accompanying disclosure, including the drawing which graphically illustrates the subject invention. In at least one embodiment of the practices of this invention at least one of the objects of this invention will be achieved.

Cellular reduced glutathione, i.e. the co-substrate for GSTs, and GST activity in general, i.e. total activity estimated using 1-chloro-3, 4-dinitrobenzene (CDNB) as a substrate, has been shown to be involved in the mechanism of chemotherapeutic drug resistance, see Johnston et al, J. Natl. Can. Inst. 82: 776-779 (1990) and Lai G-M, et al, J. Natl. Can. Inst. 81: 535-539 (1989).

Chemotherapeutic agents, such as chlorambucil cisplatin, nitrosoureas and other chemotherapeutic drugs that can damage DNA or other cellular macromolecules, such as RNA or protein, are electrophiles which can be conjugated with glutathione directly or indirectly via GST activity. Hence, high levels of glutathione and/or GST activity provide a mechanism of drug resistance because cells having high levels have increased opportunities to remove the drugs before the drugs can cause genotoxicity or cytotoxicity or other adverse effects. Heretofore, however, it has not been known whether any one of the known GST isozymes, either the alpha, pi or the mu class, is more specifically involved in conjugating chemotherapeutic drugs with glutathione.

BRIEF DESCRIPTION OF THE INVENTION

It has now been discovered, and it is the basis of this invention, that GST mu isozymes are specifically and preferentially involved in the metabolism of chemotherapeutic drugs. In accordance with this invention it has now been discovered that by measuring GST mu activity, one can estimate and/or measure an individual's resistance to chemotherapeutic drugs.

The mu class of GSTs are distinguished by having a high substrate specificity towards trans-stilbene oxide, see Seidegard, J.-E. et al, Biochem. J. 246: 783-785 (1987). About 50% of the human population lack GST mu because of a gene deletion, see Seidegard, J.-E. and Pero, R.W., Genet. 69: 66-68 (1985) and Seidegard et al Proc. Natl. Acad. Sci. U.S.A. 85: 7293-7295 (1988). Individuals can be easily phenotyped for the presence (+) or absence (--) of GST Mu activity. Because GST mu activity represents at least 60% of the total GST activity in liver, see Warholm, M. et al, Biochemistry 22: 3610-3617 (1983), and since the liver is the main source of metabolism of xenobiotic substances, including chemotherapeutic drugs, and since GST mu has been shown to have high substrate specificity toward toxic agents, such as trans-stilbene oxide, benzopyrene 4,5-oxide and ethylene oxide, but little substrate specificity for other GST substrates, such as cis-stilbene oxide

and 1-chloro-2,4-dinitrobenzene, see Seidergard, J.-E. et al, Carcinogenesis 6: 1121-1216) 1985, GST mu activity may be employed to estimate a genetic based sensitivity of individuals to metabolize chemotherapeutic drugs.

BRIEF DESCRIPTION OF THE DRAWING

The single FIGURE is a graph in which glutathione transferase activity toward tauromustine is plotted against glutathione transferase activity toward trans-stilbene oxide.

DETAILED DESCRIPTION OF THE INVENTION

The following example is illustrative of the practices of this invention. In the example tauromustine, a nitrosourea, a class of chemotherapeutic drugs, was metabolized to a much greater extent by human liver cytosols having GST mu activity than by human liver cytosols lacking GST mu activity. The data illustrated in the accompanying drawing teach that the presence (+) or absence (--) of GST mu can predict individual sensitivity to chemotherapeutic drugs, such as nitrosoureas, which damage DNA.

EXAMPLE

The importance of the GST-tSBO phenotype in influencing drug metabolism is indicated by the following. Tauromustine is a drug representative of the class of chemotherapeutic agents known as the nitrosoureas and has the structural formula:

[GRAPHIC]

Human liver biopsies from ? 3 individuals were homogenized in 5 vol. of 0.25 M sucrose, centrifuged at 10,000 g for 15 minutes and then the resulting supernatant was re-centrifuged at 105,000 g for one hour. The 105,000 g supernatants were analyzed for glutathione transferase activity using trans-stilbene oxide (tSBO) and tauromustine as substrates. Metabolism of these substrates to glutathione conjugates was monitored by radiometric procedures involving differential organic solvent extraction, see Gill, S., Ota, J. and Hammock, B., D. Anal. Biochem. 131: 273-282 (1983), and high pressure liquid chromatography (HPLC).

The results are graphically presented in the accompanying drawing. When GST-tSBO activity in liver cytosols was 0-10 nmo/min/mg protein, the level of glutathione transferase activity toward tauromustine was also very low ranging from 0-2 nmol/min/mg protein. However, when there was easily detectable GST-tSBO activity, i.e. 25-65 nmol/min/mg proteins, there was also substantial metabolism of tauromustine (i.e. 4-19 nmol/min/mg protein).

As mentioned hereinabove, there are at least three different classes of human glutathione transferases, the alpha, mu and pi classes. Each class is composed of several isozymes and GST-tSBO has been determined to be a distinct isozyme of the mu class. Hence, these data teach that the metabolism of nitrosoureas, such as are represented by tauromustine, is mainly carried out by GST-tSBO, identical to GST-mu, and not by the other isozymes of glutathione transferase. It follows then, since GST-tSBO activity has been shown to be under genetic control and to be absent in about 50% of the population with a higher degree of resistance to chemotherapy, such as to chemotherapeutic drugs represented by the nitorsoureas.

The embodiment of this invention recognizes the prior knowledge that glutathione and total GST activity, usually measured with CDNB as substrate, can contribute to drug resistance. However, CDNB can serve as a substrate for all the GST ioszyme sub-groups (i.e. alpha, pi and mu classes), and it was not obvious or recognized that any single GST isozyme was contributing more than any other to drug metabolism. Moreover, the pi class of GST isozymes had been the only GST to be more directly implicated in chemotherapeutic drug resistance, see Moscow, J.A. and Cowan, K.H., J. Natl. Can. Inst. 80: 14-20 (1988)

and even then, only in relation to reduced glutathione levels. In other words, the selective metabolism of a chemotherapeutic drug by GST pi isozymes, or any other GST other than GST mu, shown in Example 1, has not been demonstrated. This has implied that the substrate specificity of GSTs is very broad and the various classes of GSTs can metabolize drugs in a reasonably equal manner. Therefore, it was unexpected that GST mu isozymes could contribute so dramatically to chemotherapeutic drug resistance in individuals expressing GST Mu activity compared to individuals lacking GST mu activity, even though both GST mu (+) and (--) individuals have other classes of GST activity present.

Although the expression of the GSTs is organ specific, the expression of GST mu is known to be controlled by genetic factors where about 50% of the population has no GST mu activity. None of the other human GSTs have been shown to be lacking in such a large portion of the population, nor have they been shown to have a high degree of substrate specificity controlled by genetic factors. The combination of these GST mu characteristics, together with the demonstrated selective metabolism of nitrosoureas by GST mu show that the GST mu phenotype can be predictive of chemotherapeutic drug resistance via metabolism characterized by a selective conjugation with glutathione catalyzed or brought about by GST mu.

In the practices of this invention testing of a person's GST mu activity can be carried out by obtaining and testing the blood samples of the human to be tested as well as tissue or organ samples, such as the liver, colon, breast and adrenal glands. Particularly useful, from the point of view of convenience in carrying out the tests and determinations in accordance with this invention, would be to carry out the tests on the person's mononuclear leukocytes. All the tests would be carried out employing trans-stilbene oxide as the substrate for the glutathione transferase since trans-stilbene oxide is a specific substrate for glutathione transferase GST mu. The level of glutathione transferase activity towards trans-stilbene oxide would be measured as nmol/mn/mg protein and level of four (4), especially a level higher than eight (8), would be indicative that the person so tested for glutathione transferase mu activity would posses substantial drug resistance and would not be a good candidate for drug therapy or cancer chemotherapy and the like, even when the person so tested might evidence glutathione transferase activity of the GST alpha and pi classes.

Instead of using tSBO as a substrate to phenotype individuals for GST mu affinity and thus drug resistance, other ways of determining GST mu activity may be employed. For example the (+) or (--) GST mu activity can also be determined by using antibodies derived from purified GST mu or a DNA probe derived from or based on the GST mu gene.

All the above-cited publication references are herein incorporated and made part of this disclosure.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many modifications, alterations and substitutions are possible in the practices of this invention without departing from the spirit or scope thereof.

What is claimed is:

1. A method of determining the resistance of a human individual to a nitrosourea which comprises determining the GST mu activity of the individual, to establish a measured value of the individual's GST mu activity, and comparing said measured value with a predetermined value, the presence of a GST mu activity above said predetermined value indicting that the individual is resistant to the nitrosourea.

2. A method according to claim 1, wherein the determining step is performed using tSGO to
measure the individual's GST mu activity.

3. A method according to claim 1, wherein the determining step is performed using an antibody to GST mu to measure the individual's GST mu activity.

4. A method according to claim 1, wherein the determining step is performed using a labeled DNA probe for the GST mu gene to measure the individual's GST mu activity.

5. A method according to claim 1, wherein the determining step is performed by testing liver tissue of the individual.

6. A method according to claim 1, wherein the determining step is performed by testing colon tissue of the individual.

7. A method according to claim 1, wherein the determining step is performed by testing breast tissue of the individual.

8. A method according to claim 1, wherein the determining step is performed by testing mononuclear leukocytes of the individual.

9. A method according to claim 2, wherein the determining step is performed by testing liver tissue of the individual.

10. A method according to claim 2 wherein the determining step is performed by testing mononuclear leukocytes of the individual.

11. A method according to claim 1 wherein to said measured value of GST mu activity is measured towards tSBO, nmol/min/mg protein, and said predetermined value is 4 or above.

12. A method according to claim 1 wherein said nitrosourea is tauromustine.

13. A method of determining the resistance of a human individual to tauromustine, comprising determining GST mu activity of liver tissue of the individual using tSBO, to establish a measured value of said activity expressed in nmol/min/mg protein and comparing said measured value with a value of 4, a measured value above 4 indicating that the individual is resistant to tauromustine.

* * * * *

406057.1

[GRAPHIC]
US005340565A

United States Patent Patent Number: 5,340,565

Pero Date of Patent: Aug. 23, 1994

TUMOR OR CANCER CELL KILLING THERAPY AND AGENTS USEFUL THEREFOR

Inventor: Ronald W. Pero, New York, N.Y.

Assignee: Oxi-Gene, Inc., New York, N.Y.

Appl. No.: 896,236

Filed: June 10, 1992

Related U.S. Application Data

Continuation of Ser. No. 89,477, Aug. 25, 1987.

Int. Cl. A61K 49/00; G01N 33/15
U.S. Cl. 424/10; 424/649
Field of Search 424/10; 649; 514/619

References Cited

U.S. PATENT DOCUMENTS

5,081,153 1/1992 Pathak et al. 424/649

OTHER PUBLICATIONS

White et al., "Induction Chemotherapy for Advanced Head and Neck Cancer...," Am. J. Clin. Oncol. (CCT), 15(1) (1992), pp. 45-55.
S. Lybak et al., "Dose schedule evaluation of metoclopramide...," Anti-Cancer Drugs 2: 375-82 (1991).
R. J. Nelt et al., "Phamacokinetis of Non-Protein-Bound Platinum Species...," Cancer Treat. Rep. 63: 1515-21 (1979).
J. Hansson et al., "Cis-Diamminedichloroplatinum (II) Toxicity...," Acta Oncologica 27: 383-92 (1988).
K.C. Micetich et al., "A Comparative Study of the Cytotoxicity...," Cancer Research 45: 4043-47 (1985).
L.A. Zwelling et al., "DNA-Protein and DNA Interstrand Cross-Linking...," Cancer Research 39: 365-69 (1979).
C.A. Perez et al., "Impact of Irradiation Technique and Tumor Extent...," Cancer 50: 1091-99 (1982).
E. Kjellen et al., "Metoclopramide enhances the effect of cisplatin...," Br. J. Cancer 59: 247-50 (1989).
E. Kjellen et al., "A therapeutic benefit from combining normobaric carbogen...," Radiotherapy and Oncology 22: 81-91 (1991).
S. Lyback, Metoclopramide: A representative of a new class of drugs for potentiation of cytotoxicity, University of Lud, Sweden (1991), p. 115.

Primary Examiner -- Nathan M. Nutter
Attorney, Agent, or Firm -- Cooper & Dunham

406050.1

ABSTRACT

The effectiveness of cytostatic and/or cytotoxic drugs and/or radiation in the killing of tumor and/or cancer cells is increased by the administration, along with said drugs and radiation, of an effective activating or inhibiting amount of a compound or agent which activates or inhibits the chromatin-bound enzyme adenosine diphosphate ribosyl transferase (ADPRT) or the administration of an effective intracellular free Ca++-increasing amount of a compound which induces cellular or oxidative stress or which acts as an inhibitor or antagonist or calmodulin or Ca++-calmodulin binding. Suitable such compounds or agents include the phenothiazines, antihistamines, butyrophenones, cannabinoids and corticosteriods and particularly metoclopramide when employed in combination with cisplatin.

7 Claims, 1 Drawing Sheet

[GRAPHIC]

406050.1

TUMOR OR CANCER CELL KILLING THERAPY AND AGENTS USEFUL THEREFOR

This is a continuation of application Ser. No. 089,477, filed Aug. 25, 1987.

BACKGROUND OF THE INVENTION

One important strategy in designing effective cancer chemotherapeutic drugs is defining the mechanism of cell death. Activation of the chromatin-bound enzyme, adenosine diphosphate ribosyl transferase (ADPRT), and the subsequent depletion of energy metabolites, such as NAD and ATP, are involved in the suicidal response to induced cellular DNA damage that leads eventually to cell death, Berger, N.A., J. Clin. Invest. 78: 1131-1135, 1986.

Radiation and/or most cancer therapeutic drugs induce DNA damage, and as a consequence involve ADPRT activity as part of their cytotoxic mechanisms of action, Huet and Laval, Int. J. Radiat. Biol. 47: 655-662, 1985.

Hence, inducers of ADPRT enhance cytotoxicity by seriously depleting cellular energy pools in an effort to repair the potentially lethal DNA damage induced by most chemotherapeutic drugs and/or radiation. This is true because NAD is consumed as a co-substrate by ADPRT activity, Hayaishi and Ueda, Ann. Rev. Biochem. 46: 96-116, 1977; Purnell et al., Biochem. Soc. Trans. 8:215-227, 1980, which is in turn induced by DNA strand breaks, Halldorsson et al., FEBS Lett. 85: 349-352, 1978; Benjamin and Gill, J. Biol, Chem. 255:10493-10508, 1980; Cohen and Berger, Biochem. Biophys. Res. Commun. 98: 268-274, 1981. since cellular NAD/ATP pools are coupled, then cellular energy is depleted and cytotoxicity is enhanced. On the other hand, inhibitors of ADPRT are also sensitizers of cytotoxicity because they prevent the repair of potentially lethal DNA damage.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows the effect of treatment of the growth of a human squamous cell carcinoma xenographed to nude mice with CDDP (CiS-Diamine-Dichloroplatinum) combined with Metoclopramide.

The invention is indicated in accompanying FIG. 1 wherein data demonstrating the effectiveness of a practice of this invention is graphically illustrated.

SUMMARY OF THE INVENTION

This invention relates to the discovery that many compounds with antiemetic action, such as the substituted N-tertiary amino benzamides, phenothiazines, antihistamines, butyrophenones, cannabinoids, and corticosteriods have properties that enhance the effectiveness of cytostatic drugs or radiation in the killing of tumor cells. Broadly, compounds which activate or inhibit the chromatin-bound enzyme adenosine diphosphate ribosyl transferase ADPRT or which induce cellular or oxidative stress or which act as inhibitors or antagonists of calmodulin or Ca++-calmodulin binding are useful to enhance the effectiveness of cytostatic drugs or radiation in the killing of tumor cells.

DETAILED DESCRIPTION OF THE INVENTION

There are at least 4 well known classes of inhibitors of ADPRT; namely nicotinamide analogs, benzamide analogs, pyrazinamide analogs and purine analogs, Sims et al., Biochem. 21: 1813-1821, 1982, Nduka et al., Eur. J. Biochem. 105: 525-530, 1980. The common structural feature that was shown to be of importance to maintain a high degree of inhibition of ADPRT by the analogs of nicotinamide, benzamide and pyrazinamide, is the presence of a ring-carboxamide group. For example, benzoic acid, 3-aminobenzoic acid, pyrazine 1,2-dicarboxylic acid, isonicotinic acid, and 6-amino nicotinic acid all failed to inhibit ADPRT, Sims et

al., Biochem. 21: 1813-1821, 1982. Therefore, judging from an experimental point of view it would not be obvious that N-tertiary amino substitutions of the carboxamide residue of benzamide analogs would result in derivatives that can modulate ADPRT. In fact, the only known pharmacological/biological effects reported in the scientific literature for these analogs are as antiemetic agents, see U.S. Pat. No. 3,177,252, and for review see also Weiss and Weintraub, Drug Ther. 12: 167-170, 1982 and Reich, S. O., Cancer Nurs. 6: 71-73; 1983).

Nicotinamide, benzamide, 3-aminobenzamide and purine analogs, such as theophylline and other xanthines, have been shown to be effective sensitizers of the cytotoxic action induced by radiation and cancer chemotherapeutic drugs in both cell culture and animal tumor model systems, Ben-Hur, E., Int. J. Radiat. Biol. 46: 659, 1984; Utsumi and Elkind, Brit. J. Cancer (suppl. 6):39, 1984; Calcutt et al., Brit J. Cancer 24: 380, 1970; George et al., Int. J. Radiat. Biol. 49: 783, 1986; Thraves et al., Int. J. Radiat. Oncol, Biol. Phys. 12:1541, 1986; Thraves et al., Int. J. Radiat. Res. 104:119, 1985; Thraves et al., Int. J. Radiat. Biol. 50:961, 1986; Kumor et al., Int. J. Radiat. Biol. 47:1C3, 1985, Huet and Laval, Int. J. Radiat. Jonsson et al., Cancer Res. 45:3609, 1985; Kjelle'n et al., Acta Radiologica 25:281, 1986; Horsman et al., Int. J. Radiat. Oncol. Biol. Phys. 12:1307, 1986; Horsman et al., Radiat. Res. 109:479, 1987; Nduka et al., Eur. J. Biochem. 105:525, 1980; Mourelatos et al., Mutation Res. 121:147, 1983. However, with the exception of nicotinamide, all of these classes of sensitizers are quite toxic by themselves thereby limiting their potential development for use in humans. Furthermore, relatively high doses were required for sensitizing either cells (millimolar concentration) or tumor bearing animals 100 mg/kg) to radiation or cancer chemotherapeutic drugs.

Nicotinamide will radiosensitize an adenocarcinoma transplanted in C3H mice at a dose of 10 mg/kg whereas benzamide is totally ineffective in this dose range, Kjelle'n and Pero, Eight International Symposium on ADP-ribosylation, May 30 - June. 3, 1987, Forth Worth, Tex., Abstract 76. The low dose effectiveness of nicotinamide has been attributed to an active transport mechanism for which benzamide can only partially and poorly compete, Pero et al., Eight International Symposium on ADP-ribosylation, May 30 - Jun. 3, 1987, Forth Worth, Tex., Abstract 69. However, compounds which would compete for the nicotinamide binding and transport site and which modulate ADPRT, then such compounds would be theoretically effective sensitizers of radio- and chemotherapies at non-toxic low doses. Metoclopramide (4-amino-5-chloro-N-[(2-diethylamino)ethyl]-2-methoxy-benzamide) is a drug like nicotinamide in that it sensitizes a cancer chemotherapeutic agent at the daily low dose of 2 mg/kg.

Most chemotherapeutic agents utilized in the treatment of tumors cause, among other disturbances, a gastrointestinal toxicity characterized in particular by nausea and vomiting. These symptoms are important in that they affect the patients' well-being and ability to nourish themselves and often may exercise an influence on their acceptance or refusal to continue treatment. Metoclopramide is well established as a successful antiemetic treatment for chemotherapy induced nausea and vomiting, see Reich, S.D. Cancer Nurs. 6:71-73, 1983, although several other drugs with antiemetic properties, such as phenothiazines, antihistamines, benzamide derivatives, butyrophenones, cannabinoids, and corticosteriods have ben used, Laszlo, J. Drugs 25 (Suppl. 1):1-7, 1983. However, despite the common use of metoclopramide and other antiemetics in chemotherapeutic treatment regimens, these drugs have never been evaluated in relation to the clinical effectiveness of the chemotherapeutic drug and in combination therewith.

Contrary to scientific expectations and based on benzamide analog studies as inhibitors of ADPRT and thus sensitizers of radio- and chemo- therapies, substitutions into the carboxamide group of benzamide, nicotinamide and pyrazinamide analogs, do not necessarily destroy the sensitizing properties of these compounds since metoclopramide, a polysubstituted-N-tertiary amino alkyl benzamide, is an effective sensitizer in cancer chemotherapy, such as a sensitizer of a cancer chemotherapeutic drug.

The following are examples of the practices of this invention.

EXAMPLE 1

Cisplatin (cis-diamine-dichloroplatinum = CDDP) is a heavy metal complex with alkylating properties which allow bifunctional linking to DNA. CDDP has been used successfully as a chemotherapeutic agent to treat several types of human cancers. Since CDDP treatment regimes induce nausea and vomiting, metoclopramide is often co-administered therewith as an antiemetic drug. This example demonstrates that metoclopramide not only suppresses the number of episodes of nausea and vomiting, but it also potentiates the cytotoxic effect of CDDP on human cancer cells, such as on a human squamous cell carcinoma (SCC) (ABII) of the head and neck xeno-grafted to nude mice.

Two administration schedules were tested: (A) metoclopramide (2.0 mg/kg i.p.) one hour before CDDP (7.5 mg/kg i.p.) and (B) metoclopramide (2.0 mg/kg X 3 treatment times) given separately concomitant to CDDP (7.5 mg/kg i.p.) and 24 hr. and 48 hr. after CDDP administration. In both schedules the combined treatment was compared with CDDP alone, metoclopramide alone and with physiologic saline treated tumor bearing animals (controls). The tumor line used was a poorly differentiated human SSC originating from the nose. There were n=10 animals in each group. Tumor diameters and animal weight were recorded and plotted twice weekly for 21 days. Treatment efficacies were compared using the area under the plotted growth curves (AUC).

There was no mortality and no weight loss of significance in any treatment group. In neither schedule A nor B did metoclopramide alone induce any significant reduction in AUC. CDDP alone gave a significant reduction of AUC-values. In schedule A the addition of metoclopramide did not give any additive effect. In schedule B metoclopramide potentiated the effect of CDDP, which when given alone reduced AUC to 72% of control tumor growth. CDDP + metoclopramide significantly reduced AUC to 36% of control tumor growth. The above experiment was repeated using another human SSC (EH) transplanted in nude mice. The tumor weights at day 21 after the initiation of the experiment are graphically presented in FIG. 1. Likewise, a significant reduction in tumor weight was achieved with a combined treatment of CDDP + metoclopramide. These data show that metoclopramide sensitizes or enhances the cytotoxic action of CDDP against two different human SSC lines carried in nude mice, and at a dose currently being administered as an antiemetic agent to patients receiving cancer chemotherapy.

As mentioned above, inhibitors of ADPRT enhance the cytotoxicity induced by radiation and cancer chemotherapeutic drugs. However, it is also important to appreciate that DNA strand damaging agents induce ADPRT activity and DNA damage is a target site for the biological induction of cytotoxicity, Durkacz et al., Nature 296: 593-596, 1980, and as cited above. Therefore, both inhibitors and inducers of ADPRT are potential sensitizers of the cytotoxic action of drugs, e.g. (A) inhibitors because they prevent the removal of potentially lethal DNA damage of ADPRT directed DNA repair mechanisms and (B) inducers because they enhance the production of drug- or radiation-induced DNA damage by altering the endogenous cellular mechanisms that lead to DNA damage and the subsequent activation of ADPRT. The following example presents one such mechanism of endogenous DNA damage induction valid in general for many of the drugs with antiemetic properties.

The free cytosolic level of Ca++ is known to be a critical event in the mechanism of cytotoxicity, Trump and Berezesky, Role of Sodium and Calcium Regulation in Toxic Cell Injury, in Drug Metabolism and Drug Toxicity, J.R. Mitchell and M.G. Horning (eds), Raven-Press, New York, pp 261-300, 1984, and agents that induce oxidative stress increase intracellular free Ca++ which is, in turn, modulated by the Ca++ binding protein calmodulin, Mirabelli et al., J. Biochem. Toxicol. 1: 29-39, 1986; and Means and Dedman, Nature 285: 73-77, 1980. Hence, antagonists of Ca++-calmodulin binding or agents that increase free cytosolic Ca++, such as oxygen radicals produced by oxidatively stressing the cell, would be expected to increase DNA damage, thereby activating ADPRT and inducing cytotoxicity by a mechanism different from that associated with an inhibition of ADPRT and DNA repair, Schraufstatter et al., J. Clin. Invest. 76:1131-1139, 1985, and Schraufstatter et al., J. Clin. Invest. 77:1312-1320, 1986.

The following Example II establishes that many antiemetic agents can modulate cellular Ca++ homeostasis, activate ADPRT, induce cytotoxicity in themselves and thus possess the properties to sensitize or enhance or increase cytotoxicity when used in combination with radiation and/or cancer chemotherapy drugs. Although some antiemetic agents are known to antagonize Ca++-calmodulin binding, Hidaka H. and Hartshorne D.J. (eds) Calmodulin Antagonists and Cellular Physiology, Academic Press, Inc. New York, pp. 1-543, 1985), they are not known to induce ADPRT or to enhance cytotoxicity.

EXAMPLE II

Human mononuclear leukocytes (HML) were isolated by Isopaque-Ficoll gradient centrifugation from heparinized peripheral blood samples as already described (Boyum, A., Scand. J. Clin. Lab. Invest. 21 (Suppl. 7):7, 1968. The HML were adjusted to 1 X 106 cells per ml of Eagles minimum essential medium and cultured at 37(degree) C. for 30 min in the presence or absence of the indicated doses of the compounds shown in accompanying Table 1. Either physiologic saline or 95% ethanol 0.5%, v/v) were used as co- solvents. Cytotoxicity was assessed by trypan blue exclusion either after the 30 min incubation period or after 18 hr incubation at 37(degree) C. of parallel cultures as already described, Pero et al., Mutation Res. 83:271-289, 1981. ADPRT activity was always estimated after the 30 min exposure and incubation in permeabilized cells as described previously, Pero et al., Chem. Biol. Interactions 47:265-275, 1983. Briefly, HML were permeabilized, exposed to 250 uM NAD tritium-labelled in the adenine moiety (20-25 Ci/mMol, Amersham, diluted 875:1 with cold NAD) for 15 min at 30(degree) C., and the protein-bound ADP-ribose collected onto nitrocellulose filters following precipitation with 10% trichloroacetic acid (TCA). The data were recorded as cpm TCA precipitable [3H]NAD per 1 X 106 cells.

W-7, see footnote to Table 1, is a well characterized calmodulin antagonist which has an IC50 does of around 50uM whereas W-5, a closely related structural analog, is inactive at 50 uM and it has an IC50 of about 250 uM Hidaka et al, Proc. Natl. Acad. Sci. U.S.A. 78:4354-4357, 1981. These two compounds have been used effectively to distinguish calmodulin modulated biological events, e.g. inhibition of cell proliferation, phosphodiesterase and myosin light chain kinase. Hence, W-7 and W-5 were used to determine the effect of calmodulin mediated cellular events on ADPRT activity and cytotoxicity. The data in accompanying Table 1 clearly show that W-7 induces ADPRT activity and this effect is paralleled by an increase in cytotoxicity. No such effects were observed with W-5, indicating that Ca++-calmodulin antagonism is an important endogenous mechanism for mediating cytotoxic responses and cytotoxicity can be induced by agents that antagonize Ca++- calmodulin binding.

TABLE I

Activation of ADPRT and resultant cytotoxicity induced by agents that modulate Ca++ homeostasis in HML.

Agents	Concentration (uM)	ADPRT Activity(a)	% Dead Cells(a) 30 min	% Dead Cells(a) 18 hr
(1) Controls	0	385	less than 5%	less than 5%
	0	350	less than 5%	less than 5%
(2) W-7(b)	50	750	10%	--
	100	910	25%	--
	200	1480	90%	--
(3) W-5(c)	50	395	less than 5%	5%
	100	415	less than 5%	5%
	200	425	7%	--
(4) H2O2	100	1800	5%	40%
	300	2700	5%	41%
	500	2900	7%	55%
	1000	3000	12%	71%
(5) Metoclopramide(d)	500	530	7%	8%
	2000	703	13%	29%
	5000	950	10%	58%
	10000	870	22%	88%
(6) Chlorpromazine(e)	100	1508	50%	--
	500	890	100%	--
(7) Trimeprazine(f)	100	639	7%	--
	500	571	95%	--
(8) Dixyrazine(g)	100	385	13%	78%
	500	850	79%	100%
(9) Haloperidol(h)	100	655	6%	--
	500	746	60%	--
(10) Moperone(i)	100	529	5%	--
	500	712	7%	--
	1000	1112	26%	100%

a The average of duplicate determinations are presented
b W-7 = N-(-6-aminohexyl)-5-chloro-1-naphthalenesulfonamide
c W-5 = N-(-6-aminohexyl)-naphthalenesulfonamide
d Metoclopramide = 4-amino-5-chloro-N-[C2-diethylamino)ethyl]-2-methoxybenzmide
e Chlorpromazine = 2-chloro-N, N-dimethyl - 10H-phenothiazine-10-propanimine piperazinyl]ethoxy]-ethanol
h Haloperidol = 4-[4(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone
i Moperone = 1-(4-fluorophenyl))-4-[4-hydroxy-4(4-methyl phenyl)-1-piperidiayl]-1-butanone

The importance of cellular Ca++ homeostasis in the induction of ADPRT and cytotoxicity is further supported by the data recorded for H_2O_2 in Table 1. H_2O_2 is well known to induce a Ca++ efflux from plasma membranes and mitochondria thus elevating intercellular free Ca++, imbalancing Ca++ homeostasis and inducing cytotoxicity, Mirabelli, et al, J. Biochem. Toxicol. 1:29-39, 1986. Again the data clearly indicate that H_2O_2 induces ADPRT which is paralleled by increases in interphase cell death, although the cytotoxicity is more evident after 18 hr incubation than immediately after exposure (i.e. 30 min). The data confirm thatgents which interfere with Ca++ homeostasis can also enhance cytotoxicity, and therefore these types of compounds are potential sensitizers of radiation and chemotherapeutic drugs.

The data reported in Table 1 on metoclopramide confirm this hypothesis. The data reported in Example I demonstrate that metoclopramide is a good sensitizer of the chemotherapeutic drug, cisplatin, and Table 1 establishes that metoclopramide activates ADPRT and induces cytotoxicity endogenously without the addition of other cytostatic agents. Since the other classes of agents presented in Table 1 are known modulators of Ca++ homeostasis and they, in turn, gave similar patterns of induction of ADPRT and cytotoxicity, it is concluded that these common biochemical/biological effects are characteristic of a new class of sensitizers of radiation and chemotherapeutic drugs, all as described herein. These common biochemical/biological effects are characteristic of a new class of sensitizers of radiation and chemotherapeutic drugs and are totally unexpected since metoclopramide is a benzamide derivative and benzamide derivatives have previously only been shown to sensitize cytostatic agents by inhibition of ADPRT. Consequently, Example II reveals that many antiemetic agents possess the common property of inducing ADPRT and cytotoxicity presumably via modulation of Ca++ homeostasis thus giving these agents the potential to sensitize the cytostatic action of other agents, such as radiation and chemotherapeutic drugs.

Compositions useful in the practices of this invention include in their make-up a cytotoxic or cytostatic compound or agent and a compound or agent which activates or inhibits ADPRT and/or which induces cellular or oxidative stress, such as a compound which produces or yields cellular H_2O_2 or which acts as an inhibitor or antagonist of calmodulin or Ca++-calmodulin binding.

Useful cytotoxic or cytostatic compounds or agents include, in addition to cisplatin, the other useful chemotherapeutic cytotoxic agents employed in cancer chemotherapy, such as adriamycin, 5-fluorouracil, methotrexate, cytoxan, vincristine, daunomycin, BCNU, CCN, MeCCNU and others.

Useful compounds or agents which activate or inhibit ADPRT or which induce cellular or oxidative stress or which act as inhibitors or antagonists of calmodulin of Ca++-calmodulin binding include metoclopramide, chlorpromazine, trimeprazine, dixyazine, halperidol, moperone, W-7 and W-5. The recently discovered parathyroid hormone factor, PTH-like peptide, a factor which induces high blood levels of calcium, see Science, Vol. 237, pages 363,364, July 24, 1987, also is usefully employed in compositions of and in the practices of this invention.

As indicated hereinabove, the compounds or agents which activate or inhibit ADPRT or which induce cellular or oxidative stress or which act as inhibitors or antagonists of calmodulin or Ca++-calmodulin binding and the associated cytotoxic or cytostatic agent employed in combination therewith may be administered to the human patient undergoing treatment simultaneously, separately or combined in the same composition, or substantially simultaneously, such as one compound or agent before the other or within the period of time of 1- 120 minutes, more or less, after administration of the first compound or agent of the combination. These administrations, usually intravenously, may be continued over an extended period of time of days, weeks or months.

Compositions in accordance with the practice of this invention which are usefully employed for inhibiting, controlling or reducing in humans the growth of human tumor or cancer cells by administration alone or in combination with radiation therapy contain an effective amount of a cytotoxic or cytostatic compound or agent in the range 0.1-20 parts by weight or mols and an effective amount of a compound or agent which

activates or inhibits the chromatin-bound enzyme adenosine diphosphate ribosyl transferase ADPRT or which induces cellular or oxidative stress or which acts as an inhibitor or antagonist of calmodulin or Ca++-calmodulin binding in the range 0.1-20 parts by weight or mols. The above-mentioned amounts of these compounds present in the compositions of this invention are relative to each other, i.e. for every 0.1-20 parts by weight or mols of one compound there is present a corresponding amount in the range 0.1-20 parts by weight or mols of the other compound.

Such compositions are administered by the usual or conventional techniques, e.g. orally, intramuscularly, intravenously or subcutaneously, usually depending upon the character of the cytotoxic or cytostatic compound present in the composition and the nature, amount and location of the tumor or cancer cells being treated. The amount or dosage of such compositions administered also depends up on the character of the cytotoxic or cytostatic compound in the composition as well as the character of the other compound making up the composition of this invention, the amount and/or nature of the tumor or cancer cells being treated and the extent or degree of inhibition of the tumor or cancer cells desired.

Although compositions in accordance with this invention usually contain a compound which activates or inhibits ADPRT in an amount in the range 0.1-20 parts by weight or mols, compositions which contain such compounds in an amount outside this range are also useful. For example, compositions which contain compounds which activate ADPRT in an amount in the range 0.01-12 parts by weight or mols or, for example, an amount in the range 0.5-2.0, are also useful. Compositions which contain these same amounts or ratios of the other compound, i.e. compounds which induce cellular or oxidative stress which act as inhibitors or antagonists of calmodulin or Ca++-calmodulin binding are also useful in the practices of this invention.

Although emphasis in the disclosures of this invention has been placed on the use of these compositions for inhibiting in humans the growth of tumor or cancer cells, compositions of this invention which contain substantially only a compound or agent which induces cellular or oxidative stress or which acts as an inhibitor or antagonist of calmodulin or Ca+++-calmodulin binding, are also useful. For example, such special compositions in accordance with this invention which contain a compound or agent which induces cellular or oxidative stress or which acts as an inhibitor of calmodulin or Ca++-modulin binding without a cytostatic or cytotoxic drug or with the substantial absence therein of a cytostatic and/or cytotoxic drug, are useful in the treatment of human patients undergoing radiation therapy for inhibiting the growth or tumor or cancer cells.

Indeed, in accordance with yet another embodiment of the practices of this invention such compositions which do not contain a cytostatic and/or cytotoxic drug are useful in the long term treatment of humans for the prevention of caner. Such long term treatment would extend over a period of many months and years, with regular small dosages to the human patient of a composition in accordance with this invention which contains a compound or agent which induces cellular or oxidative stress or which acts as an inhibitor or antagonist of calmodulin or Ca++-calmodulin binding. Such compositions when employed for long term treatment for the prevention of cancer in humans might also contain a small clinically ineffective amount of a cytotoxic or cytostatic drug. This aspect of this invention, however, for the prevention of human cancer is presently less preferred than the use of compositions which contain substantially only a compound or agent which induces cellular or oxidative stress or which acts as an inhibitor or antagonist of calmodulin or Ca++-calmodulin binding.

As will be apparent to those skilled in the art in the light of the foregoing disclosures, many modifications, substitutions and alterations are possible in the practices of this invention without departing from the spirit or scope thereof.

What is claimed is:

1. A method of inhibiting or killing tumor or cancer cells in a human patient which comprises treating the patient with a chemotherapeutic agent or radiation while administering to the patient an N-substituted benzamide, that can activate ADPRT, in an amount effective to increase the cytotoxicity of the chemotherapeutic agent or the radiation.

2. A method according to claim 1, which comprises treating the patient with radiation while administering to the patient an N-substituted benzamide, that can activate ADPRT, in an amount effective to increase the cytotoxicity of the radiation.

3. A method according to claim 2, wherein said N-substituted benzamide, that can activate ADPRT, is metoclopramide.

4. A method according to claim 1, which comprises treating the patient with a chemotherapeutic agent while administering to the patient an N-substituted benzamide, that can activate ADPRT, in an amount effective to increase the cytotoxicity of the chemotherapeutic agent.

5. A method according to claim 4, wherein said N-substituted benzamide, that can activate ADPRT, is metoclopramide.

6. A method of inhibiting or killing tumor or cancer cells in a human patient which comprises treating the patient with a chemotherapeutic agent or radiation while administering to the patient, in combination, nicotinamide and an oxidative stressing agent in amounts that, in combination, are effective to increase the cytotoxicity of the chemotherapeutic agent or the radiation.

7. A method of inhibiting or killing tumor or cancer cells in a human patient which comprises treating the patient with a chemotherapeutic agent or radiation while administering to the patient (a) an N-substituted benzamide, that can activate ADPRT, in an amount effective to increase the cytotoxicity of the chemotherapeutic agent or the radiation or (b) in combination, nicotinamide and an oxidative stressing agent in amounts that, in combination, are effective to increase the cytotoxicity of the chemotherapeutic agent or the radiation.

* * * * *

[GRAPHIC]
US005482833A

United States Patent Patent Number: 5,482,833

Pero et al. Date of Patent: Jan. 9, 1996

TEST TO DETERMINE PREDISPOSITION OR SUSCEPTIBILITY TO DNA ASSOCIATED DISEASES

Inventors: Ronald W. Pero, New York; Daniel G. Miller, Scarsdale, both of N.Y.

Assignee: Preventive Medicine Institute, New York, of N.Y.

Appl. No.: 430,326

Filed: Apr. 26, 1995

Related U.S. Application Data

Continuation of Ser. No. 869,823, Apt. 15, 1992, abandoned, which is a continuation of Ser. No. 333,841, Apr. 3, 1989, abandoned, which is a continuation of Ser. No. 820,203, Jan. 17, 1986, abandoned.

Int. Cl(6).....C12Q 1/68; A61K 48/00; A61K 49/00

U.S. Cl.....435/6; 435/4; 435/15; 435/29; 435/173.1; 435/820; 436/501; 436/63; 436/64; 436/813; 436/815; 514/2; 514/44; 536/22.1; 536/25.3; 935/77

Field of Search.....435/4, 6, 15, 29, 435/173.1, 820; 436/501, 63, 64, 813, 815; 514/2, 44; 536/22.1, 25.3; 935/77

References Cited

U.S. PATENT DOCUMENTS

4,585,736 4/1986 Dolbeare et al. 435/6

FOREIGN PATENT DOCUMENTS

3336786 3/1985 Germany.....435/15

OTHER PUBLICATIONS

Pero et al. (1985) Carcinogenesis, vol. 6, No. 7, pp. 1055-1058.
Pero et al. (1985) Mutation Res., vol. 142, pp. 69-73.
Biological Abstracts 78 (7) 55503.
Biological Abstracts 80 (2) 13747.
Chemical Abstract 105: 19647.
Chemical Abstract 105: 95311.

406078.1

Davis et al., Microbiology including Immunology and Molecular Genetics, 3rd ed., pp. 186-189 (1980).
Robbins, Pathologic Basis of Disease, pp. 148-152 (1974).
Simic et al., Mechanisms of DNA Damage and Repair, pp. 164-165 and 357-363 (1986).
Weisburger, J. "Bioassays and Tests for Chemical Carcinogens," Chemical Carcinogens, 1976, chapter 1, pp. 1-23.

Primary Examiner -- W. Gary Jones
Assistant Examiner -- Ardin H. Marschel
Attorney, Agent, or Firm -- Cooper & Dunham

ABSTRACT

Cellular DNA repair enzyme activity has been found to be an indicator of susceptibility or predisposition of an individual to DNA associated diseases. The activity of the enzyme adenosine diphosphate ribosyl transferase (ADPRT) has been found to be a good indicator as to the susceptibility of an individual to DNA associated diseases, such as cancer.

23 Claims, 1 Drawing Sheet

406078.1

406078.1

TEST TO DETERMINE PREDISPOSITION OR SUSCEPTIBILITY TO DNA ASSOCIATED DISEASES

This is a continuation of application Ser. No. 869,823 filed Apr. 15, 1992, which is a continuation of Ser. No. 333,841 filed Apr. 3, 1989, which is a continuation of application Ser. No. 820,203, filed Jan. 17, 1986 (all now abandoned).

BACKGROUND OF THE INVENTION

This invention relates to DNA associated diseases, such as cancer. In one aspect of this invention, this invention relates to a method for determining the level of cellular DNA repair enzyme activity. In another aspect, this invention relates to a method for monitoring the level of activity of cellular DNA repair enzymes in response to a stress. In another aspect, this invention relates to a method for screening individuals for the predisposition to cancer or other diseases associated with DNA damage. In yet another aspect, this invention relates to a method for screening therapeutic agents which may be useful for treating individuals with a predisposition to or a disease associated with DNA damage.

Most living cells possess systems for recognizing and eliminating DNA damage. As used herein, the term "DNA damage" refers to strand breaks, dimerization, unpaired bases, modified bases, conversion of one base into another resulting in unpaired bases, chromatin unwinding or other modifications, etc. For example, E coli possesses a variety of enzymes for responding to DNA damage, such as enzymes of the SOS repair system and the various Rec proteins. These enzymes, and others, respond to DNA damage caused by U.V. radiation, chemical mutagens and the like. However, little is known about the mechanism by which the repair systems are activated by DNA damage.

In addition to the prokaryotic enzymes discussed above, eucaryotic and mammalian cells are also known to possess DNA repair enzymes. These enzymes are important in controlling diseases associated with DNA damage, as is clearly shown in the disease Xeroderma pigmentosum (Xp). This recessive disease results in hypersensitivity to sunlight, particularly to ultraviolet radiation. The disease is the result of a faulty excision repair system. Fibroblasts from Xp patients are deficient in the ability to excise and correct thymine dimers and other adducts. The deficit has been shown to be in enzymes that function at the excision step of repair. Another disease correlated with faulty DNA repair is Bloom's disease, in which an increased frequency of chromosomal aberrations is seen.

DNA repair synthesis has been studied in cancer patients, see particularly the article by R.W. Pero et al. entitled "Reduced Capacity for DNA Repair Synthesis in Patients with or Genetically Predisposed to Colorectal Cancer", JNCI, Vol. 70, No. 5, pp. 867-875, May, 1983, and the article by R.W. Pero et al. entitled "Unscheduled DNA Synthesis in Mononuclear Leukocytes from Patients with Colorectal Polyps", Cancer Research, Vol. 45, pp. 3388-3391, July, 1985. These articles are of interest to the practices of this invention as applied to the measurement of the activity of DNA repair enzymes as being an indicator of the predisposition or susceptibility of an individual to colorectal cancer.

DNA damage, as indicated herein, may be caused by a number of agents. For example, oxygen supplied at concentrations greater than those of normal air has long been known to damage plants, animals and aerobic bacteria, see J.D. Balantine, Pathology of Oxygen Toxicity, 1982, Academic Press, New York. It has been proposed that many of the damaging effects of O2 could be attributed to the formation of O2 radicals, see D.L. Gilbert (ed) Oxygen and Living Processes: An Interdisciplinary Approach, 1981, Springer Verlag, New York. The reactive oxygen species are superoxide, H2O2 and a hydroxyl radical. These are generated in vivo, i.e. endogenously in the body, as a consequence of normal metabolism; see B. N. Ames, Science, 221: 1256-1264, 1983. The oxidation of certain cellular components by these oxygen species could, in turn, contribute both to aging and to age-dependent diseases, such as cancer; see P.A. Cerutti, Science, 227:375-380, 1985.

H_2O_2 is produced by all viable cells; see Romasarma, Biochem Biophysica Acta, 694:69-93, 1982, and it can be both a mutagen/carcinogen or promoter; see Troll & Wiesner, Ann. Rev. Pharmocol. Toxicol. 25:509-528, 1985, depending upon the cell type. The molecular response of a cell to stress whether it be induced by hyperthermia or by H_2O_2 is very similar; see Christman et al, Cell 41:753-762, 1985.

The practice of this invention in one embodiment employs H_2O_2 as an agent for oxidative stress to produce cellular DNA damage, thereby to induce a cellular DNA repair enzyme response, such as a response of the DNA repair enzyme adenosine diphosphate ribosyl transferase (ADPRT).

ADPRT is a nuclear enzyme which covalently attaches ADP-ribose moieties derived from NAD to chromatin proteins; see Hayoishi and Ueda, Ann. Rev. Biochem. 46:96-116, 1977 and Purnell et al., Biochem. Soc. Transa. 8:215-227, 1980. The enzyme is dependent on DNA and is strongly stimulated by DNA-strand breaks; see Halldorsson et al., FEBS LETT. 85:349-352, 1978; Benjamin and Pill. J. Biol. Chem. 255:10493-10508, 1980; Cohen and Berger, Biochem. Biophys. Res. Commun. 98:268-274, 1981. Although the role of ADPRT in cells is not fully understood, convincing data have been reported in its involvement in DNA repair; see Durkacz et al., Nature 283:593-596, 1980; Zwelling et al., Biochem. Biophys. Res. Commun. 104:897-902, 1982; Althaus et al, Biol. Chem. 257:5528-5535, 1982; Chreissen and Shall, Nature 296:271-272, 1982 and Pero et al., Chem. Biol. Interact. 47:265-275, 1983. The involvement of this enzyme in cellular differentiation is reported by Farzaneh et al., Nature 300:262-266, 1982; Johnstone and Williams, Nature 300:368-370, 1982); and Pero et al. Carcinogenesis 6:1055-1058, 1985. The involvement of this enzyme in gene expression is mentioned by Althaus et al., Nature 300:366-368, 1982 and in connection with longevity by Pero et al., Mutation Res. 142:69-73, 1985. All these cellular events are important to the process of carcinogenesis and thus are important potential regulators of individual sensitivity or risk to develop cancer.

Although, as indicated herein, H_2O_2 has been known to be produced by viable cells and to have both carcinogenic and promoting properties, it has never been shown to directly activate ADPRT in eucaryotic cells. Moreover, interindividual variation in stress-induced ADPRT, such as oxidative, e.g. H_2O_2 stress-induced ADPRT, was not known nor was any link to cancer or DNA associated disease susceptibility previously known. In the development of this invention there has been observed in 100 uM H_2O_2-induced ADPRT measured values, a greater than 50-fold variation in the cell population tested.

The disclosures of the above-identified publications are herein incorporated and made part of this disclosure.

It is an object of this invention to provide a method whereby individuals with a predisposition to diseases associated with DNA damage could be recognized. Upon recognition, such individuals might then beneficially receive more frequent diagnostic examinations, pretreatment with drugs and the like.

It is also an object of this invention to provide a method for measuring the activity of DNA repair enzymes, particularly ADPRT activity.

It is also an object of this invention to provide a method for screening agents for potential therapeutic value for the treatment of individuals predisposed to diseases associated with the activity of DNA repair enzymes, such as the activity of ADPRT.

How these and other objects of this invention are achieved will become apparent in the light of the accompanying disclosure made with reference to the accompanying drawing which graphically illustrates the relationship of cancer patients and those with a positive family history of cancer or a negative family history of cancer with the measured ADPRT activity of such individuals.

SUMMARY OF THE INVENTION

In accordance with this invention a method has been developed to determine the predisposition or susceptibility of an individual to DNA associated disease. This method involves subjecting the cellular DNA of the individual to stress to induce or bring about DNA damage. The activity of the cellular DNA repair enzymes, particularly ADPRT activity, is then measured and the measured enzyme activity is then compared against a given or predetermined value to determine the relative predisposition or susceptibility of the tested individual to DNA associated disease, such as cancer. A measured value of cellular DNA repair activity, such as ADPRT activity, below said given value would indicate a greater susceptibility or predisposition to DNA associated diseases compared to an individual having a measured value above said given value.

BRIEF DESCRIPTION OF THE DRAWING

The Figure illustrates patient or family history relationships of cancer to measured ADPRT activity.

Section (A) of the Figure is a graph illustrating the relationship of cancer patients with the measured ADPRT activity of such individuals;

Section (B) of the Figure is a graph illustrating the relationship of persons with a positive family history of cancer with the measured ADPRT activity of such individuals; and

Section (C) of the Figure is a graph illustrating the relationship of persons with a negative family history of cancer with the measured ADPRT activity of such individuals.

DETAILED DESCRIPTION OF THE INVENTION

The method of this invention for identifying an individual with a predisposition or susceptibility to diseases associated with the activity of DNA repair enzymes comprises isolating a cell, such as a mononuclear leukocyte or an epithelial or a fibroblast cell from the individual to be tested, stressing the cell to damage the cellular DNA structure to produce a stressed cell containing damaged cellular DNA and then determining a value for the ADPRT activity in the stressed cell. The measured value of ADPRT is then compared to the value of ADPRT activity in a cell from a so-called normal individual or a given value of ADPRT activity. A significant decrease in the activity of the enzyme ADPRT in the stressed cell would indicate a predisposition of the individual from whom such cells were taken and tested to DNA associated disease, such as cancer, relative to another individual whose cells, when so tested, show a higher measured DNA repair enzyme activity, such as ADPRT activity.

A variety of agents associated with causing DNA structural damage may be used in the practice of this invention to stress the cell to be tested to induce DNA damage. Those agents which cause oxidative stress are preferred, such as hydrogen peroxide, cumene hydroperoxide and benzoyl peroxide. Other agents usefully employed include xanthine, xanthine-oxidase, phorobol diesters and bleomycin. Radiation, such as ultraviolet radiation, gamma radiation or x-ray radiation, may also be employed to induce cellular DNA damage.

As indicated hereinabove, in the practices of this invention as an indicator of DNA repair enzyme activity it is preferred to measure the value of ADPRT activity in a cell containing damaged DNA. In the preferred practice of this invention the activity of ADPRT is measured as counts per minute (cpm) of 3H-NAD per 1 x 106. The cells to be tested, as indicated herein, could be isolated from a variety of tissues. Presently preferred cells for testing in accordance with the practice of this invention are the mononuclear leukocytes, fibroblasts or epithelial cells but other DNA containing cells may also be employed. The activity of ADPRT in the cell is determined by contacting the cell with hydrogen peroxide to produce a stressed cell

containing damaged DNA, followed by measuring the activity of the ADPRT in the stressed cell to obtain a value for ADPRT activity. The value so obtained is compared with a predetermined value of at least about 1200 cpm 3H-NAD per 1 x 106 cells, such as a value in the range of 3500-4500 cpm 3H-NAD per 1 x 106 cells. A significant difference of the measured value from the predetermined value would indicate that the cell so tested provides a modified cellular ADPRT activity.

In another embodiment of the practice of this invention there is presented a method for screening therapeutic agents for the treatment of individuals predisposed to diseases associated with DNA or the activity of DNA repair enzymes. The method comprises isolating a cell from a predisposed individual, stressing the cell with an agent to produce cellular DNA damage and with a therapeutic agent to produce a resulting stressed and treated cell. The activity of the DNA repair enzymes, such as ADPRT activity in the stressed and treated cell, is then determined to obtain a value of ADPRT activity and this value is compared against a predetermined value or a value obtained from a stressed cell which has not been treated with said therapeutic agent. If the ADPRT activity value of the stressed but untreated cell is less than the ADPRT value of the stressed and treated cell, this result would indicate that the tested therapeutic agent may be effective for the treatment of the predisposed individual.

The following is an example illustrative of the practice of this invention:

EXAMPLE

ADPRT is the only known biological reactant that consumes the ADP moiety of NAD. Accordingly, if NAD is radiolabeled in the adenine moiety, the trichloracetic acid (TCA)-precipitable radioactive counts would reflect ADPRT activity via (ADP-ribose) polymerization to chromatin proteins. The protocol used to measure ADPRT activity is a modification of the procedure of Berger (D.M. Prescott ed.), Methods in Cell Biology 20:325-400, 1978 and is published in detail by Pero et al. in Chem Biol Interactions 147, 265-275, 1983.

ADPRT activity was measured as follows: Peripheral blood samples (20 ml) were collected by venous puncture into heparinized tubes (10-20 USP units/ml) from 24 individuals with diagnosed cancer of the lung, colon or pancreas, from 25 individuals with at least a first degree relative having either lung, colon or pancreas cancer and from 21 individuals with no family history of cancer. The mononuclear leukocyte fraction was isolated from the whole blood samples by density gradient centrifugation at 400XG for 20 minutes after layering on top of an Isopaque Ficoll cushion at a density of 1.077 gm/ml.

Duplicate cultures of 1-5x106 cells were incubated with or without either a standardized dose of either 100 uM H_2O_2 in 1.0% autologous plasma supplemented physiological saline for 60 minutes at 37(degree) C. The resulting mixtures were removed at the end of the incubation period by centrifugation. The cells (+) and (-) H_2O_2 treatment were permeabilized, adjusted to 0.5x106 cells per treatment and ADPRT activity estimated after 15 minutes at 30(degree) C. in a reaction mixture containing 175 uM (161.6 uCi/mmol) of [3H] adenine-labeled NAD. The data were recorded as TCA precipitable [3H]-NAD per 1x106 cells which were collected onto nitrocellulose filters. The (-) H_2O_2 ADPRT values were then subtracted from the (+) H_2O_2 values.

The results of these tests are graphically indicated in the accompanying drawing. As shown in the drawing, it can be seen that the frequency distribution of individual values for 100 uM H_2O_2 induced ADPRT varied in accordance with either the occurrence or the genetic predisposition to develop cancer. For example, when 100% of the values for the cancer patients were below ADPRT values of 2300, 72% of the individuals with a positive family history of cancer were below 2300 while the corresponding value for the group with no family history of cancer was 38%, all as indicated in the accompanying drawing. These results, as shown and quantified in the drawing, can usefully predict an individual's risk or predisposition or susceptibility to DNA associated disease, such as cancer.

Although in the practices of this invention it is preferred to measure directly ADPRT activity by the technique disclosed in the Example described hereinabove involving the measurement of TCA precipitated radiolabeled protein, the measurement of ADPRT activity can also be carried out indirectly through its effect or influence upon other DNA repair enzymes, such as topoisomerase, ligase and endonuclease and other related DNA associated enzymes, such as polymerase and exonuclease. The activities of these enzymes as affected by the activity of ADPRT can be separately measured by suitable techniques involving, as may be appropriate, radiolabeled components or monoclonal antibodies to components or products of the activity of such enzymes, particularly as may be influenced or effected by the activity of ADPRT.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many modifications, alterations and substitutions are possible in the practices of this invention without departing from the spirit or scope thereof.

What is claimed is:

1. A method for identifying an individual with a predisposition to diseases associated with the activity of DNA repair enzymes which comprises stressing cells of said individual to produce stressed cells containing damaged DNA, thereby to cause induced activity of adenosine diphosphate ribosyl transferase (ADPRT) in the stressed cells, determining a value for the induced activity of the ADPRT in the stressed cells, and comparing the value so determined with a reference value of the activity of ADPRT to ascertain whether said value so determined is higher or lower than said reference value, a determined value lower than said reference value identifying said individual as having said predisposition.

2. A method in accordance with claim 1 wherein the cell is subjected to stress by exposure to radiation.

3. A method in accordance with claim 1 wherein said cells are stressed by ultraviolet radiation.

4. a method in accordance with claim 1 wherein said cells are stressed by x-ray radiation.

5. A method in accordance with claim 1 wherein the cells are subjected to oxidative stress.

6. A method in accordance with claim 5 wherein said oxidative stress involves exposure to hydrogen peroxide.

7. A method in accordance with claim 5 wherein said oxidative stress involves exposure to cumene hydroperoxide.

8. A method in accordance with claim 5 wherein said oxidative stress involves exposure to benzoyl peroxide.

9. A method in accordance with claim 5 wherein said oxidative stress involves exposure to xanthine-xanthine oxidase.

10. A method in accordance with claim 1 wherein the cells are subjected to stress by contact with phorbol esters.

11. A method in accordance with claim 1 wherein the cells are subjected to stress by contact with bleomycin.

12. A method in accordance with claim 1 wherein the activity of ADPRT is measured as cpm 3H-NAD per 1x106 cells.

13. A method in accordance with claim 1 wherein said cells are mononuclear leukocytes.

14. A method in accordance with claim 1 wherein said cells are fibroblasts.

15. A method in accordance with claim 1 wherein said cells are epithelial cells.

16. A method for screening therapeutic agents suitable for the treatment of individuals predisposed to diseases associated with DNA which comprises stressing cells of an individual to produce DNA damage, thereby to cause induced activity of adenosine diphosphate ribosyl transferase (ADPRT) in the stressed cells, contacting or treating the resulting stressed cells with a therapeutic agent to produce resulting stressed and treated cells, determining a value for the induced activity of the ADPRT in the resulting stressed and treated cells, and comparing the value so determined with a predetermined value to evaluate the effectiveness of the therapeutic agent for the treatment of said individual by ascertaining whether said obtained value is higher or lower than said predetermined value, an obtained value higher than said predetermined value indicating that the therapeutic agent is effective for the treatment of said individual.

17. A method of testing an individual for a predisposition to a disease associated with DNA damage, comprising stressing DNA-containing cells of the individual to produce stressed cells having damaged cellular DNA, thereby to cause induced activity of adenosine diphosphate ribosyl transferase (ADPRT) in the stressed cells, determining a value for the induced activity of ADPRT in the stressed cells, and comparing the value so determined with a reference value of ADPRT activity to ascertain whether said value so determined is higher or lower than said reference value, wherein said predisposition is indicated if said value so determined is lower than said reference value.

18. A method according to claim 17, wherein said cells are mononuclear leukocytes, epithelial cells, or fibroblast cells.

19. A method according to claim 18, wherein said cells are mononuclear leukocytes.

20. A method according to claim 17, wherein said disease is cancer.

21. A method according to claim 20, wherein said disease is cancer of the colon, liver or pancreas.

22. A method for testing the immune competency of an individual, comprising stressing DNA-containing cells of the individual to produce stressed cells having damaged cellular DNA, thereby to cause induced activity of adenosine diphosphate ribosyl transferase (ADPRT) in the stressed cells, determining a value for the induced activity of ADPRT in the stressed cells, and comparing the value so determined with a reference value of ADPRT activity to ascertain whether said value so determined is higher or lower than said reference value, wherein a low immune competency with respect to a disease associated with cellular DNA damage is indicated if said value so determined is lower than said reference value.

23. A method for testing the efficacy of a therapeutic agent for treating an individual for a disease associated with DNA damage, comprising stressing DNA-containing cells of the individual to produce stressed cells having damaged cellular DNA, thereby to cause induced activity of adenosine diphosphate ribosyl transferase (ADPRT) in the stressed cells, determining a value for the induced activity of ADPRT in the stressed cells, and comparing the value so determined with a reference value of ADPRT activity to ascertain whether said value so determined is higher or lower than said reference value, wherein said cells are cells

treated with said agent, and wherein efficacy of said agent is indicated when said determined value is higher than said reference value.

* * * * *

406078.1

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION [GRAPHIC]
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification6: G01N 21/00 A1

(11) International Publication Number WO96/14565

(43) International Publication Date: 17 May 1996 (17.05.96)

(21) International Application Number: PCT/IB95/01019

(22) International Filing Date: 18 October 1995 (18.10.95)

(30) Priority Data:
08/330,015 27 October 1994 (27.10.94) US

(71) Applicant: OXiGENE, INC. [US/US]; 110 East 59th Street, New York, NY 10022 (US).

(72) Inventor: PERO, Ronald, W.; Staffan's Grand 6A, S-222 23 Lund (SE).

(74) Agent: DUNHAM, Christopher, C.; Cooper & Dunham LLP, 1185 Avenue of the Americas, New York City, NY 10036 (US).

(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG) ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD OF TESTING IMMUNE COMPETENCY

(57) Abstract

A method of testing the immune competency of an individual be determining, from a sample of the blood of the individual, a value for total plasma/serum thiols including both protein thiols and nonprotein thiols, and comparing the value so determined with a reference value of total plasma/serum thiols to ascertain whether the determined value is higher or lower than the reference value, a determined value lower than the reference value being indicative of impaired immune function.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Cote d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

406048.1

METHOD OF TESTING IMMUNE COMPETENCY

BACKGROUND OF THE INVENTION

This invention relates to methods of testing human individuals for impaired immune function indicative of the presence of, or predisposition to, diseases associated with compromised immune competency. Such tests may be used, for example, diagnostically, prognostically, and as a guide in determining the need for preventive or therapeutic treatment for the disease or condition so indicated.

More particularly, the invention employs a surrogate measure of DNA repair activity based on serum/plasma thiol status as a biomarker of human health. Thus, the method of the invention involves the measurement of chemically reactive thiols present in naturally occurring amino acids, polypeptides and proteins found in human serum or plasma. The concentration of these thiols can predict DNA repair capacity and immune cell responsiveness, and they are therefore useful indicators of disease progression where impaired immune function is an essential component of the disease. HIV infection, AIDS, cancer and autoimmune disorders are examples of diseases that have immunological components.

European patent No. 0 229 674 as well as several recently published papers (Pero et al, Carcinogenesis 6:1055-58, 1985; Pero et al, Mutation Res. 142:69-73, 1985; Pero et al, Carcinogenesis 10:693-97, 1989; Pero et al, Carcinogenesis 10:1657-64, 1989) disclose that DNA repair in general, and specifically the quantitative estimation of adenosine diphosphate ribosyl transferase (ADPRT) , is a useful endpoint to estimate health risks in the detection, prevention and treatment of human chronic age-associated diseases such as cancer, conditions that predispose to cancer, and autoimmune diseases. In another aspect, cellular ADPRT activity has been shown to relate to immune cell responsiveness (Scouvassi et al, Carcinogenesis 8:1295-1300, 1987; Pero et al, J. Neurosurg. 77:601-06, 1992; Johnstone and Williams, Nature 300:368-79, 1982; Johnson et al, Int. J. Biochem. 22:67-73, 1990), and both these parameters have been shown to be modulated by the cellular

reduction/oxidation (redox) balance thought to be in turn mediated by the thiol containing peptide, glutathione (Pero et al, Cancer Det. Prevent. 14:555-61, 1990; Pero et al, Cancer Res. 50:4619-25, 1990; Fidelius et al, Exp. Cell Res. 170:269-75, 1987; Fidelius and Tsan, Immunology 61:503-08, 1987; Fischman et al, J. Immunol. 127:2257-62, 1981; Hamilos and Wedner, J. Immunol. 135:2740-47, 1985).

Glutathione exists in the millimolar range within cells (Kosower, Int. Rev. Cytol. 54:109-60, 1978; Meister, Science 220:472, 1983) and as such it is believed to be the primary cellular reductant protecting cells from oxidative cellular injury. However, glutathione levels in human serum/plasma (i.e. 2-27 umoles/liter in Buhl et al, The Lancet, 1294-98, December 2, 1989; Ayers et al, Anal. Biochem. 154:186-93, 1986) represent only a minor portion of the total reactive thiol groups present because the proteins in serum/plasma constitute the major source of reactive thiol groups (i.e. 113-133 umoles/liter in Ellman, Arch. Biochem. Biophys. 82:70- 77, 1959 and Ayers et al, Anal. Biochem. 154:186-93, 1986). Therefore, the art teaches that there are at least two distinct classes of thiols in serum/plasma and other biological tissues; namely protein thiols and nonprotein thiols. A review of the literature supports that conventional procedures for the analysis of serum/plasma thiols in relation to human health consequences are based on the analysis of nonprotein thiol sources such as glutathione or cysteine where protein thiols are excluded from the analysis by the assay procedure or removed by precipitation using agents such as trichloroacetic acid, metaphosphoric acid, sulfosalicylic acid or perchloric acid before any analysis of nonprotein thiols is undertaken (Beutler and Gelbert, J. Lab. Clin. Med. 105:581-04, 1985; Buhl et al, The Lancet, 1294-98, December 2, 1989; Eck et al, Biol. Chem. Hoppe Seyler 370:101-81, 1989; Burgunder et al, Eur. J. Clin. Invest. 18:420-24, 1988; Burgunder and Lauterburg, Eur. J. Clin. Invest. 17:408-14, 1987; Mimic-Oka et al, Biochem. Med. Met. Biol. 39:48-54, 1988; Martensson, Metabolism 35:118-21, 1986; Vendemiale et al, J. Hepatology 9:359-65, 1989). Nonprotein thiol analysis of biological samples has evolved as the standard assay procedure principally because of the strong scientific belief that glutathione, a nonprotein thiol, is the primary cellular reductant protecting cells against the harmful health effects of oxidant injury (Meister, Science 220:472, 1983).

Oxidative cellular damage has been postulated to be an important factor in (i) ageing (Harmon, Age 7:111-31, 1984), (ii) diabetes (Wilson et al, Diabetologia 27:587-91, 1984), (iii) drug resistance (Spitz et al, J. Cell Physiol. 156:72-9, 1993), HIV+/AIDS (Baruchel and Wainberg, J. Leuk. Biol. 52:111-14, 1992), (iv) initiation and promotion of cancer (Marnett, Carcinogenesis 8:1345-73, 1987; Cerutti, Science 227:375-81, 1985), (v) etiology of cardiovascular and autoimmune diseases (Cross et al, Ann. Int. Med. 107:526-45, 1987) and (vi) modulation of immune function (Carson et al, J. Exp. Med. 163:746-51, 1986). Most of this evidence comes from evaluating oxidative stress by comparing glutathione deficient to glutathione proficient cells. For example, glutathione (or cysteine, its synthetic precursor) deficiency has been shown to (i) predispose cells to increased sensitivity to DNA damage (Edgren et al, Int. J. Rad. Biol. 40:355-63, 1985; Valis, The Lancet 337:918-19, 1991), (ii) inhibit DNA repair (Pero et al, Cancer Res. 50:4619-25, 1990; Edgren and Revesz, Int. J. Rad. Biol. 48:207-12, 1985), or (iii) induce immune cell response deficiency (Hamilos and Wedner, J. Immunol. 135:2740-47, 1985; Fischman et al, J. Immunol. 127:2257-62, 1981; MacDermott et al, Immunology 57:521-26, 1986; Droege et al, Immunobiology 172:151-56, 1986; Stacey and Craig, Experienta 45:180-81, 1989). In other words, the art teaches that the nonprotein thiol component is the important factor relating oxidative cellular damage to human disease development, and the protein thiol component, which quantitatively dominates in biological samples, has no direct or regulatory relevance to the health consequences of redox imbalance, and if it indicates anything at all, it is an indirect and nonspecific estimate compared to the major regulatory role of the nonprotein thiol component.

Additional evidence for this interpretation is taken from the medical literature where serum/plasma thiols have been employed to monitor health disorders. Malignant disease (Beutler and Gelbert, J. Lab. Clin. Med. 105:581-84, 1985), chronic renal insufficiency (Mimic-Oka et al, Biochem. Med. Met. Biol. 39:48-54, 1988), glucose mediated insulin secretion (Ammon et al, Diabetologia 32:797-800, 1989), ethanol ingestion (Burgunder et al, Eur. J. Clin. Invest. 18:420-24, 1988; Vendemiale et al, J. Hepatology 9:359-65, 1989), fasting (Martensson, Metabolism 35: 118-21, 1986), HIV infection (Buhl et al, The Lancet, 1294-98, December 2, 1989), AIDS (Eck et al, Biol. Chem. Hoppe Seyler, 370:101-08, 1989), and cirrhosis (Burgunder

and Lauterburg, Eur. J. Clin. Invest. 17:408-14, 1987) represent nearly all the medical conditions where serum/plasma thiols have been used successfully to monitor health disorders. In all cases, serum/plasma nonprotein thiols such as glutathione or cysteine were estimated, and great care was taken to eliminate protein thiols from the assay procedure. These data clearly indicate that it was not obvious to one skilled in the art to include serum/plasma protein thiols in the analyses, or that they might be indicators of the health consequences of oxidative stress, as good as, or even better than, the nonprotein thiols.

Congestive heart failure (Belch et al, Br. Heart J. 65:245-48, 1991) and rheumatoid arthritis (Pullar et al, Br. J. Rheumat. 26:202-06, 1987) are the only exceptions found in the scientific literature where both serum/plasma protein and nonprotein thiols were included in the final analyses. However, the logic behind these exceptions did not indicate that total serum/plasma protein and nonprotein thiols were a better indicator of the health consequences of oxidative cellular damage than were serum/plasma nonprotein thiols. Contrarily, it was postulated in these studies that because serum/plasma albumin was an important factor to these diseases, and because albumin is the major protein component of serum/plasma and contains numerous thiol functions, it followed that estimating total serum/plasma protein and nonprotein thiols was an effective surrogate measure of the oxidation state of albumin. Therefore, the inclusion in the serum/plasma thiol assay of nonproteins such as glutathione or cysteine and proteins other than albumin added no significant methodological advantage even though they were included in the final analyses and contaminated the estimation of albumin thiols.

SUMMARY OF THE INVENTION

The present invention broadly contemplates the provision of a method for testing the immune competency of an individual, comprising the steps of obtaining a sample of blood of an individual to be tested; determining, from the sample, a value for total plasma/serum thiols, including both protein thiols and nonprotein thiols, for the individual; and comparing the value so determined with a reference value of total plasma/serum thiols to ascertain whether the value so determined is higher or lower than the reference value, a determined

value lower than the reference value identifying the individual as having impaired immune function of significance in detecting, preventing or treating health disorders.

The invention embraces the unexpected discovery that when the quantitative analysis of protein thiols is included in the serum/plasma assay procedure, there exists a highly significant relationship to the function of cellular DNA repair, estimated as ADPRT activity, in immune proficient mononuclear leucocytes. Because DNA repair, and specifically ADPRT activity, estimates cell functions in response to oxidative cellular damage that can predict risk to immune dysfunction and age associated diseases as has already been documented in publications discussed above, this discovery establishes that total (i.e. protein and nonprotein) serum/plasma thiols serve as a quantitative surrogate assay for the estimation of DNA repair, immune function and health risk in the detection, prevention and therapy of human diseases. Therefore, total serum/plasma sulfhydryl analyses have improved sensitivity and biological relevance over assay procedures estimating only serum/plasma nonprotein thiols such as glutathione.

The invention contemplates measuring the total level of serum/plasma thiol groups present in the protein and nonprotein components, and relating the thiol level to DNA repair, immune function and to the detection, prevention and treatment of human diseases such as cancer, AIDS, autoimmune and cardiovascular disorders. Although the invention in its broader aspects is not limited to specific procedures for total serum/plasma thiol determination, in illustrative embodiments of the invention total serum/plasma thiols can be conveniently determined by spectrophotometric or fluorometric procedures involving the development of chromophores after reaction with thiols using aromatic disulfides such as DTNB (5,5'-dithiobis-2-nitrobenzoic acid), organic or inorganic oxidants such as iodosobenzoic acid, diphenyl picrylphenyl hydrazine, benzfuroxan, 4,4' dimethylaminodiphenyl carbinol, quinones, trinitrobenzenesulfonic acid, nitroprusside, ferricyanide, cupric copper, permanganate, iodine, mercurials, nitrous acid, maleimides, halides, platinum salts, palladium ions, fluorobenzoxadiazole derivatives, or papain-thiol sensitive p-nitroanilide reaction (Jocelyn, Methods in Enzymology 143:44-67, 1987; Imai, Methods in Enzymology 143:6775, 1987; Ayers et al, Anal. Biochem. 154:186-93, 1986; Singh et al, Anal. Biochem. 213:49-56, 1993). Concentration of chromophoric agent, pH,

incubation time of the reaction mixture, and state of denaturation of protein structure with agents such as sodium dodecyl sulfate, urea, or guanidinium chloride are well known variables affecting the quantification of thiols, and as such, they should be optimally controlled for each chromophoric agent and not serve as a basis to limit the scope of this invention.

In another aspect, this invention proposes to relate ADPRT activity to the serum/plasma thiol content. This is logically and theoretically accomplished by taking advantage of the facts that ADPRT is a thiol containing protein, and at least some of the thiols are located in the zinc binding domain of the enzyme which in turn controls its participation in DNA repair (Mazen et al, Nucleic Acids Res. 17:4689-98, 1989).

Therefore, ADPRT activity is dramatically up and down regulated by cellular reduction/oxidation balance which in turn is regulated and monitored by thiol status (Pero et al, Cancer Res. 50:4619-25, 1990) Furthermore, it is found that there is a natural production of ADPRT inhibitors via normal metabolic cellular processes which can inhibit DNA repair and immune cell function. These substances were identified as HOC1 and N-chloramines which are well known oxidants of thiol (Schraufstatter et al, J. Clin. Invest. 85:554-62, 1990). It is also found that most of the total serum/plasma thiols are chemically reactive with N-chloramines, and as such, this parameter can be used as a surrogate indicator of the endogenous cellular production of HOC1/N-chloramines. Because HOC1/N-chloramines produced as byproducts of cellular metabolism also inhibit DNA repair (Van Rensberg et al. , Free Radic. Biol. Med. 11:285-91, 1991) and immune function, the serum/plasma thiols reacting with HOC1/N-chloramines likewise measure the functional health consequences of oxidatively stressed cells that can occur in human disorders such as ageing, autoimmunity, cancer, cardiovascular disease, diabetes, drug resistance and HIV infection.

There are well known distinct classes of ADPRT activity; namely, constitutive, induced and activated ADPRT activities. DNA damage is a necessary cofactor that drives the ADPRT enzymatic activity (Satoh and Lindahl, Nature 356:356-58, 1992). The constitutive ADPRT level reflects the intrinsic or steady state enzymatic activity in response to endogenous cellular levels of DNA damage induction. However, the ADPRT activity can be activated by exogenously supplied DNA damaging agents, such as oxidatively stressing cells by

exposure to reactive oxygen species produced by phagocytes or chemical agents (Pero et al, Cancer Det. Prevent. 14:555-61, 1990), to maximum levels of ADPRT activity. Consequently, induced ADPRT activity (e.g. in response to oxidative stress) can be calculated by subtracting the constitutive ADPRT activity from the activated ADPRT activity. This invention also embraces the discovery that when ADPRT activity is activated by DNA damage and measured as either activated or induced ADPRT levels, the plasma thiol levels significantly estimate mononuclear leucocyte ADPRT enzymatic activity when determined in parallel on the same blood samples as are used to obtain the plasma samples.

Further features and advantages of the invention will be apparent from the detailed description hereinafter set forth, together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph in which PMA induced ADPRT in 1 x 106 HML and cellular production of HOC1 are plotted against incubation with neutrophils;

FIG. 2 is a graph having two portions in which PMA induced ADPRT activity in HML is plotted against uM of Chloramine T and of HOC1, respectively;

FIG. 3 is a three-part graph in which absorbance units at 412 nm are plotted against H202 activated ADPRT for total plasma thiol groups, N-chloramine insensitive plasma thiol groups, and N-chloramine sensitive plasma thiol groups;

FIG. 4 is another graph similar to FIG. 3; and

FIG. 5 is a graph illustrating a serum thiol surrogate ADPRT test for HIV positive and HIV negative patient groups.

DETAILED DESCRIPTION

The method of the invention for testing the immune competency of a human individual comprises the steps of obtaining a sample of the blood of the individual to be tested; subjecting the sample to an assay for determining a value for total (protein + nonprotein) serum/plasma thiols for the individual; and comparing the value so determined to a reference value to ascertain whether the value so determined is higher or lower than the reference value, a determined value lower than the reference value identifying the individual as having impaired immune function.

The assay typically includes initially deriving, from the obtained blood sample, a sample of serum or plasma, and determining a value for total thiols (i.e., both protein thiols and nonprotein thiols) in the serum or plasma sample by a spectrophotometric or fluorometric procedure involving the development of chromophores after reaction with thiols using a suitable chromophoric agent, as discussed above. Such procedures, in themselves well known in the art, provide a measurement or reading, e.g. in absorbance units at 412 nm, representing a determined value of total plasma/serum thiols for the individual.

The determined value is then compared with a reference value for indicating whether the individual being tested does or does not have impaired immune function in accordance with whether the determined value of the individual's total serum/plasma thiols is below or above the reference value. That is to say, in accordance with the present invention it has now been found that, for any procedure for assaying total (protein + nonprotein) serum/plasma thiols of an individual, there exists a reference value such that a determined value for an individual's total serum/plasma thiols below that reference value identifies the individual as having impaired immune function.

The establishment of an appropriate reference value to function as an indicator of impaired immune function will be readily apparent to persons skilled in the art from the foregoing description. For instance, the reference value can be established by testing a number of individuals of known immune competency (impaired and unimpaired) to determine a range of values of total serum/plasma thiols of such individuals, and identifying the lower limit of the range (or selecting a point, related thereto, providing a desired confidence level of

impaired or unimpaired immune function determination) as the reference value. Such a reference value is illustrated in Example 5 described below, as the lower limit of total serum thiols of an HIV (normal immune competency) patient group. FIG. 5, representing data obtained in Example 5, shows that among HIV+ patients tested, some had determined values of total serum thiols above this reference value, and others had determined values of total serum thiols below the reference value. Within the investigatory period, fatalities occurred only in the latter (below reference value) group of HIV+ patients and not in the former (above reference value) group of HIV+ patients, substantiating the correlation between impaired immune function and determined values of total serum thiols below the reference value.

One illustrative use of the present method is as a guide to deciding whether to subject a particular patient to treatment for the condition or consequences of the impaired immune function so ascertained. For instance, in the case of HIV+ patients as represented by Example 5, those having determined values of total serum thiols below the reference value (represented by about 0.25 absorbance units at 412 nm) might be subjected immediately to such treatment while those having total serum thiol values above the reference value, indicating as-yet uncompromised immune competency, would not yet need treatment.

In a specific aspect, the method of the invention may be employed as a surrogate measure of induced ADPRT activity, which is itself an indicator of the presence of, or a predisposition to, DNA-associated diseases, as described for example in European patent No. 0 229 674.

The invention will be further described with reference to the Examples set forth below, in which the following specific procedures were employed:

Blood component preparation. -- Peripheral blood samples (n = 225) from apparently healthy volunteers, patients with predisposition for cancer and cancer patients were obtained by venous puncture and collected into heparinized vacutainers (143 USP units/10 ml tube). The blood samples were first centrifuged at 100 X G for 10 min and the platelet rich plasma removed with a Pasteur pipette. Platelet-poor plasmas to be used in these experiments were prepared by centrifuging the platelet-rich plasmas at 400 X G for 25 min to pellet the platelets. Next, the original volume of blood samples were restored by addition of physiologic saline

and then they were carefully layered on top of a commercially available density cushion (1.077 gm/ml, Organon Teknika) before spinning at 400 X G for 25 min. The human mononuclear leucocytes (HML) were isolated from the interphase zone of the density gradient, washed by centrifugation using RPMI 1640 medium and the cell density adjusted for in vitro culturing purposes in the conventional manner. When both HML and neutrophils were needed, the cell fractions were simultaneously isolated by layering the blood sample on top of neutrophil isolation medium (Cardinal Associates) , and carrying out all steps in the density gradient isolation using Krebs-Ringer phosphate buffer with glucose (KRPG, pH = 7.4) according to the procedure of Nathan (J. Clin. Invest. 80:1550-60, 1987).

Cytotoxicity. -- Regardless of the isolation method used for blood cell fractionation, HML were always resuspended in 10-20% serum or plasma supplemented RPMI 1640 medium, pelleted and then resuspended again in either physiologic saline or KRPG buffer for treatment with either HOC1 or chloramine T (Sigma). HOC1 concentration was determined from the e235 = 100 M-1cm-1. Cytotoxicity was monitored by cellular exclusion of trypan blue (0.2% isotonic solution + 5% serum) after 15 min incubation with the dye at 37 degrees C. The cytotoxicity of HOC1 and N-chloramines is well known (Schraufstatter et al, J. Clin. Invest. 85:554-62, 1990). Hence, it was important to determine that any biochemical effects on ADPRT activity induced by these agents were not related to acute cytotoxicity. The experimental conditions outlined above, and used to collect the data reported on herein, were non-acutely cytotoxic.

HOC1 measurement. -- Mixed cultures of HML + neutrophils were assayed for the production of HOC1 in the extracellular conditioned medium by removal of the cells by centrifugation following the incubation period, and immediately trapping the produced HOC1 with taurine (20 mM). Taurine chloramine was then quantified spectrophotometrically by using the conversion of I- to I2 (E = 2.29 X 104 M-1 cm-1). Details of this procedure have been described by Weiss et al (J. Clin. Invest. 70:598-607, 1982).

ADPRT assay. -- The procedure was adapted from the permeabilized cell technique of Berger (Methods Cell Biol. 20:325-340, 1988) with modifications as previously described (Pero et al, Carcinogenesis 10:1657-64, 1989). Duplicate samples of 1 x 106 HML in the presence of 0 to 4 x 106 neutrophils were cultured in 1 ml of

KRPG buffer for 30 min at 37 degrees C in the presence of PMA (phorbol-12-myristate-13-acetate, 25 ng/ml). After this co-incubation, the HML + neutrophil mixtures were harvested by centrifugation, permeabilized, and ADPRT activity determined by radiometric procedure as described in detail elsewhere (Pero et al, Carcinogenesis 10:1657-64, 1989). In other experiments, duplicate HML samples of 1 X 106 per ml KRPG buffer were directly treated with 0-100 uM dose ranges of HOC1 or chloramine T for 30 min at 37 degrees C which was then followed immediately by treatment with a standardized dose of PMA (25 ng/ml) for another 30 min before analysis of ADPRT activity as already referred to above.

Plasma/serum thiol determination. -- Plasma samples were collected from the same heparinized blood samples that were used to determine mononuclear leucocyte poly ADPRT activity. The samples were stored under liquid nitrogen until subjected to analysis. Each plasma sample was thawed and centrifuged at 2000 X G to sediment any precipitated fibrin. Two ml 20% plasma in water (i.e. 4:1 dilution of plasma with water) was prepared and 30 ul of 5,5' dithiobis-(2-nitrobenzoic acid) (DTNIB) was added as a 9.5 mg/ml solution dissolved in 0.1 M K2HPO4, 17.5 mM EDTA, pH 7.5. The mixture was left to react at room temperature for 1 hr, at which time the absorbance units at 412 nm (A412) was measured. Chloramine T (Sigma) dissolved in water was then added at a final concentration of 40 uM and the A412 again read after 30 min. Total plasma thiols as well as N-chloramine sensitive and insensitive plasma thiols were calculated by subtraction of reagent blank values from the values of total DTNB reactive and N-chloramine reactive thiols. In the study involving HIV+ (n = 15) and HIV- (n = 13) patients initiated in May 1993, the same procedure was used except serum samples were analyzed instead of plasma samples. The serum samples were donated by intravenous drug users attending the Aaron Diamond Research Center for AIDS. The sera were prepared over a period of years and biologically banked at -80 degrees until used in this study.

EXAMPLE I

This Example establishes that human phagocytes (i.e. neutrophils) produce physiologic relevant concentrations of endogenous ADPRT inhibitors. Under conditions that permit viable cell culturing, a standardized amount of HML (human mononuclear leucocytes, 1 X 106) was incubated together with increasing amounts of neutrophils from 0 to 4 X 106 cells per culture. Neutrophils do not respond to the induction of DNTA damage by an activation of ADP-ribosylation, and so these cells do not contribute to the estimation of ADP-ribosylation in this experiment (Ikai et al, Proc. 5 Natl. Acad. Sci. USA 77:3682-85, 1980). Next these combined cultures were exposed to PMA (phorbol-12-myristate-13-acetate) to activate ADP-ribosylation in HML, and to induce the production of reactive oxygen intermediates by neutrophils. The abundant reactive oxygen intermediates, hydroxyl radical, super oxide anion, and hydrogen peroxide, are all well known inducers of ADP-ribosylation (Pero et al, Cancer Det. Prevent. 14:555-61, 1990). The data in FIG. 1 show that when HML + neutrophil ratios reached 1:2 (X 106 cells/ml), which is comparable to the proportion and concentration in blood, HML ADP-ribosylation began to become severely inhibited. The respiratory burst induced by PMA exposure of neutrophils was monitored by HOC1 production. It was concluded that either the presence of neutrophils or the production of about 80 uM HOC1 or N-chloramine was sufficient to cause inhibition of HML ADP-ribosylation.

EXAMPLE 2

The effect of various dosage levels of chloramine T and HOC1 on PMA induced ADPRT activity in HML was investigated utilizing the procedures described above for such tests, measuring the PMA induced ADPRT activity for HML subjected to the various dosages, and comparing the values obtained with measured control values of PMA induced ADPRT activity in HML from the same source but with zero dosages of chloramine T and HOC1. The results, represented in FIG. 2, confirm that HOC1 and N-chloramine are potent naturally occurring ADPRT inhibitors because they can cause greater than 80% inhibition of HML (human mononuclear leucocyte) ADPRT activity at doses of 80 uM, which are levels easily attainable in peripheral blood under

culture conditions that give negligible cytotoxicity. This Example together with Example 1 clearly shows that ADPRT inhibitors are naturally produced as a by-product of the respiratory burst of phagocytes which is a normal function of this cell type designed to kill infectious agents.

EXAMPLE 3

Utilizing the above-described procedures, values were determined for H202 activated ADPRT activity in HML and for total plasma thiols, N-chloramine insensitive plasma thiols, and N-chloramine sensitive plasma thiols coming from the same blood samples (n = 225). Results are represented in FIG. 3. This Example demonstrates that plasma thiols significantly predict the level of hydrogen peroxide activated ADPRT activity determined in HML (human mononuclear leucocytes) coming from the same blood samples. Furthermore, this example shows that the N-chloramine sensitive plasma thiols give a better correlation than the N-chloramine insensitive plasma thiols to HML ADPRT activity, and that most of the N-chloramine sensitive plasma thiols are plasma protein thiols and not just nonprotein plasma thiols. Consequently, the best surrogate predictor of ADPRT activity was total protein + nonprotein plasma thiols. HOC1 and N-chloramines are efficient oxidizers of thiols, and could as such in a surrogate manner indicate ADPRT activity. The logic linking ADPRT activity to plasma thiols is based on the facts (1) that ADPRT can be dose dependently up- and down- regulated by reduced and oxidized glutathione, respectively (Pero et al, Cancer Res. 50:4619-25, 1990) and (2) that ADPRT has thiol amino acid constituents in the DNA binding domain of the enzyme which in turn control its participation in DNA repair (Mazen et al, Nucleic Acid Res. 17:4689-98, 1989).

EXAMPLE 4

Again following the above-described procedures, tests were made to compare values of H2O2 induced ADPRT in HML with values of total plasma thiols, N-chloramine insensitive plasma thiols, and N-chloramine sensitive plasma thiols from the same blood samples. Example 4 extends the knowledge disclosed in Example 3 to show that plasma thiols can also predict hydrogen peroxide HML (human mononuclear leucocyte) induced

ADPRT activity (FIG. 4). Examples 3 and 4 also teach that because the activated and induced levels of ADPRT directly relate to DNA repair in general, then plasma thiols can also be used to surrogately estimate DNA repair responses in HML.

EXAMPLE 5

The aforementioned serum samples of HIV+ and HIV- individuals were assayed by the above-described plasma/serum thiol determination procedure to determine values of total serum thiols. Results are plotted on the graph of FIG. 5.

Example 5 confirms that estimating N-chloramine sensitive serum thiols has clinical utility in that reduced levels indicate HML (human mononuclear leucocyte) ADPRT deficiency that can lead to accumulation of DNA damage and inhibition of immune function of importance in the progression of HIV+ infection to AIDS and death. The half-solid squares represent the only deaths that have occurred as of August 1993. The study was conducted in May 1993.

It is to be understood that the invention is not limited to the procedures and embodiments hereinabove specifically set forth, but may be carried out in other ways without departure from its spirit.

CLAIMS

What is claimed is:

1. A method for testing the immune competency of an individual, comprising the steps of

(a) obtaining a sample of blood of an individual to be tested,

(b) determining, from said sample, a value for total plasma/serum thiols, including both protein thiols and nonprotein thiols, for said individual, and

(c) comparing the value so determined with a reference value to ascertain whether said value so determined is higher or lower than said

reference value, a determined value lower than said reference value identifying said individual as having impaired immune function of significance in detecting, preventing or treating health disorders.

2. A method according to claim 1, wherein the determining step comprises deriving, from the obtained blood sample, a sample of serum or plasma, and subjecting the serum or plasma sample to an assay for total thiols including both protein thiols and nonprotein thiols.

3. A method according to claim 2, wherein the assay comprises a spectrophotometric or fluorometric procedure involving development of chromophores after reaction with thiols using a chromophoric agent.

4. A method for testing the immune competency of an HIV+ individual, comprising the steps of

(a) obtaining a sample of blood of an HIV+ individual to be tested,

(b) determining, from said sample, a value for total plasma/serum thiols, including both protein thiols and nonprotein thiols, for said individual, and

(c) comparing the value so determined with a reference value established by determining values for total plasma/serum thiols for HIV- individuals, to ascertain whether said value so determined is higher or lower than said reference value, a determined value lower than said reference value identifying said individual as having impaired immune function.

5. A method of testing an individual for the presence of or a predisposition to a disease associated with DNA damage, comprising

(a) obtaining a sample of blood of an individual to be tested, and

(b) subjecting the blood sample to a surrogate test for activated or induced activity of adenosine diphosphate ribosyl transferase (ADPRT) by the steps of

(i) determining, from said sample, a value for total plasma/serum thiols, including both protein thiols and nonprotein thiols, for said individual, and

(ii) comparing the value so determined with a reference value of total plasma/serum thiols corresponding to a reference level of ADPRT activity, to ascertain whether said value so determined is higher or lower than said reference value, wherein said presence of or predisposition to a disease associated with DNA damage is indicated if said value so determined is lower than said reference value.

406048.1

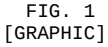
FIG. 1


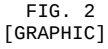
FIG. 2


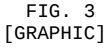
FIG. 3


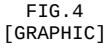
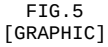
FIG.4


FIG.5


INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB95/01019

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :G 01 N 21/00,
US CL :436/64, 86, 119, 120, 164; 435/974
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/64, 86, 119, 120, 164; 435/974

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, STN
search terms: HIV or AIDS or immun; plasma or serum or blood; protein or thiol or mercapto

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF LEUKOCYTE BIOLOGY, Volume 52, issued July 1992, SYLVAIN BARUCHEL ET AL, "The role of oxidative stress in disease progression in individuals infected by the human immunodeficiency virus", pages 111-114, see page 112.	1-5
Y	Chemical Abstracts, A.E. FAUVIER,"Biological indicators of oxidative stress in humans", abstract no. 236410, Trace Elem. Free Radicals Oxid, Dis., [Proc. Int. Congr. Trace Elem. Med. Biol.], 4th (1994), pages 57-80.	1-5

/X/ Further documents are listed in the continuation of Box C. / / See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
17 MARCH 1996

Date of mailing of the international search report
11 APRIL 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

JAN M. LUDLOW

Facsimile No. (703) 305-3230

Telephone No. (703) 308-0651

Form PCT/ISA/210 (second sheet)(July 1992)*

406048.1

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CANCER RESEARCH, Volume 50, issued August 1, 1990, R. W. PERO ET AL, "Oxidative stress induces DNA damage and inhibits the repair of DNA lesions induced by N-acetoxy-2-acetylaminofluorene in human peripheral mononuclear leukocytes:, pages 4619-4625, see entire document.	5