PRO PHARMACEUTICALS INC
Form SB-2
July 17, 2003
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As filed with the Securities and Exchange Commission on July 17, 2003

Registration No. 333-

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM SB-2

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

PRO-PHARMACEUTICALS, INC.

(Name of Small Business Issuer in its Charter)

Nevada	**2834**	**04-3562325**
(State or other jurisdiction of incorporation or organization)	**(Primary Standard Industrial Classification Code Number)**	**(I.R.S. Employer Identification No.)**

189 Wells Avenue

Newton, Massachusetts 02459

(617) 559-0033

(Address and Telephone Number of Principal Executive Offices)

David Platt, Ph.D.

President and Chief Executive Officer

Pro-Pharmaceuticals, Inc.

189 Wells Avenue

Newton, Massachusetts 02459

(617) 559-0033

(Name, Address and Telephone Number of Agent for Service)

with copies to:

Jonathan C. Guest, Esq.

Perkins, Smith & Cohen, LLP

One Beacon Street

Boston, Massachusetts 02108

(617) 854-4000

Approximate date of commencement of proposed sale to the public: As soon as possible after this registration statement is declared effective.

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, 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 this Form is a post-effective amendment filed pursuant to Rule 462(d) 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, check the following box: ¨

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount Proposed to be Registered(1)(2)	Proposed Maximum Offering Price per Share	Maximum Aggregate Offering Price(2)	Amount of Registration Fee(3)
Common Stock, $.001 par value(4)	2,843,304	$4.25(5)	$12,084,042(5)	$977.60

(1) Total represents 2,843,304 shares of common stock to be offered by selling security holders of the Registrant. In the event of a stock split, stock dividend or similar transaction involving the common stock of the Registrant, in order to prevent dilution, the number of shares registered shall be automatically increased to cover additional shares in accordance with Rule 416(a) under the Securities Act.

(2) Includes 98,320 shares of common stock that remain unsold and are being carried forward from Registration Statement No. 333-74604 pursuant to Rule 429 of the Securities Act of 1933, for which a filing fee of $31 was previously paid. Upon being declared effective, this registration statement shall constitute a post-effective amendment to Registration Statement No. 333-74604.

(3) A filing fee of $31 was previously paid for the 98,320 shares of common stock carried forward from Registration Statement No. 333-74604 pursuant to Rule 429.

(4) Common stock outstanding held by selling security holders.

(5) Estimated solely for the purpose of calculating the registration fee in accordance with Rule 457(c) under the Securities Act based on the average of the high and low sales prices of the common stock on July 15, 2003, as reported on the OTC Bulletin Board.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until this Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

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The information contained in this prospectus is not complete and may be changed. The selling security holders may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED JULY 17, 2003

PRO-PHARMACEUTICALS, INC.

2,843,304 Shares of Common Stock

$.001 par value

We are registering up to 2,843,304 shares of our common stock for sale by certain shareholders of our company from time to time. The selling security holders will receive all the proceeds from the sale of the offered shares. See Selling Security Holders on page 26 of this prospectus.

Our common stock is traded on the OTC Bulletin Board under the symbol PROH . The last reported sales price of the common stock on July 15, 2003 was $4.30 per share.

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page 2 to read about certain risks you should consider before buying shares of our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

Our principal executive offices are located at 189 Wells Avenue, Newton, Massachusetts 02459. Our telephone number is (617) 559-0033.

The date of this Prospectus is .

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PROSPECTUS SUMMARY

About This Prospectus

This prospectus is part of a registration statement we filed with the U.S. Securities and Exchange Commission. You should rely on the information provided in this prospectus. Neither we nor the selling security holders listed in this prospectus have authorized anyone to provide you with information different from that contained in this prospectus. The selling security holders are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of common stock. Applicable SEC rules may require us to update this prospectus in the future.

About Pro-Pharmaceuticals, Inc.

We are engaged in research and development of drug technologies to enable targeted delivery of widely used chemotherapy drugs. We intend initially to combine our proprietary carbohydrate compounds with existing generic chemotherapy drugs used to treat cancer. We believe our technology will increase the body s tolerance to these toxic drugs by targeting the delivery directly to cancerous cells. Our company s approach of improving existing chemotherapy drugs by adding a targeting mechanism should reduce the toxicity and increase the efficacy of these drugs thereby creating a preferable treatment to existing first line regimens. Additionally, we believe that this drug development strategy will enable our company to gain patent protection on drugs we reformulate with our carbohydrate compounds.

The U.S. Food and Drug Administration (the FDA) has approved our first Investigational New Drug Application (IND) for Phase I human clinical trials relating to colorectal cancer. Additionally, the FDA also approved our amendment to broaden the scope of our IND to include all solid tumors. We have begun clinical trials of our drug and are in the process of collecting results. Also, we are currently conducting preclinical animal experiments with additional IND candidates. We have not yet generated any operating revenues.

We were incorporated under Nevada law in January 2001. Shares of our common stock currently are quoted on the OTC Bulletin Board under the symbol PROH .

Our address is 189 Wells Avenue, Newton, Massachusetts 02459. Our telephone number is (617) 559-0033, fax number is (617) 928-3450, e-mail address is foley@pro-pharmaceuticals.com, and our website address is www.pro-pharmaceuticals.com.

THE OFFERING

Common stock offered by the selling security holders:

2,843,304 shares

Common stock currently outstanding (as of May 31, 2003):	20,323,600 shares
Use of Proceeds:	We will not receive any of the proceeds from the sale of the shares owned by the selling security holders.

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RISK FACTORS

An investment in our common stock involves a high degree of risk. You should carefully consider the risks described below and the other information contained in this prospectus before deciding to invest in our common stock. The risks described below are not the only ones facing our company. Additional risks not presently known to us or which we currently consider immaterial may also adversely affect our business. We have attempted to identify below the major factors that could cause differences between actual and planned or expected results, but we cannot assure you that we have identified all of those factors. If any of the following risks actually happen, our business, financial condition and operating results could be materially adversely affected. In this case, the trading price of our common stock could decline, and you could lose part or all of your investment.

Risks Related to Pro-Pharmaceuticals

We Are At An Early Stage Of Development Without Operating History. We are a development-stage company without operating history, and we have not generated any revenues to date. We have no therapeutic products available for sale, and none are expected to be commercially available for several years, if at all. We may never generate revenue or become profitable, even if we are able to commercialize any products.

We Have Incurred Net Losses To Date And Depend On Outside Capital. Our accumulated deficit as of March 31, 2003 was approximately $8,778,098, which includes approximately $2,427,000 of various non-cash charges related to certain equity transactions. We will need to continue to conduct significant research, development, testing and regulatory compliance activities that, together with projected general and administrative expenses, we expect will result in substantial operating losses for the next several years. Accordingly, we will not be generating our own capital and will remain dependent on outside sources of financing during that time. If we are unable to raise funds from outside sources for our continuing operations, we may be adversely affected.

We may raise such capital through public or private equity financings, partnerships, debt financings, bank borrowings, or other sources. Additional funding may not be available on favorable terms or at all. If adequate funds are not otherwise available, we may curtail operations significantly. To obtain additional funding, we may need to enter into arrangements that require us to relinquish rights to certain technologies, products and/or potential markets. To the extent that additional capital is raised through the sale of equity, or securities convertible into equity, our equity holders may experience dilution of their proportionate ownership of the company.

Based on proceeds of approximately $4,311,000 received in our private placement which was completed in January 2003, of which approximately $1,088,000 was raised in 2003, proceeds of approximately $1,770,000 as of July 10, 2003 received in our recently completed private placement begun in May 2003, and approximately $1,921,000 in cash and cash equivalents as of December 31, 2002, and budgeted expenditures for the twelve-month period ending December 31, 2003 of approximately $3,700,000, we believe that we have sufficient capital to fund our operations for all of 2003 and approximately the first quarter of 2004. If actual expenses exceed our budget, however, we will need to raise additional capital sooner in order to meet our cash needs.

Our Product Candidates Will Be Based On Novel Unproven Technologies. Our product candidates will be based upon novel unproven technologies that we plan to use to apply to drugs currently used in the treatment of cancer and other diseases. Carbohydrates are difficult to synthesize, and we may not be able to synthesize carbohydrates that would be usable as delivery vehicles for the anti-cancer drugs we plan to work with.

We Have Only Recently Begun Clinical Trials And Results Are Uncertain. We have one product candidate in clinical trials. Preclinical results in animal studies are not necessarily predictive of outcomes in human clinical trials. Clinical trials are expensive, time-consuming and may not be successful. They involve the testing of potential therapeutic agents, or effective treatments, in humans in three phases (phases I, II, and III) to determine the safety and efficacy of the product candidates necessary for an approved drug. Many products in human clinical trials fail to demonstrate the desired safety and efficacy characteristics. Even if our products progress

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successfully through initial human testing, they may fail in later stages of development. We will be dependent on others to conduct our clinical trials, including clinical research organizations and, possibly, government-sponsored agencies. These trials may not start or be completed as we forecast, or may be unsuccessful.

Our Product Candidates May Not Be Successfully Commercialized. Even if our product candidates are successful in clinical trials, they may not be successfully commercialized. Potential products may be found ineffective or cause harmful side effects during preclinical testing or clinical trials, fail to receive necessary regulatory approvals, be difficult to manufacture on a large scale, be uneconomical to produce, fail to achieve market acceptance, or be precluded from commercialization by proprietary rights of third parties.

Our Lack Of Operating Experience May Cause Us Difficulty In Managing Our Growth. We have no experience in manufacturing or procuring products in commercial quantities, conducting other later-stage phases of the regulatory approval process, selling pharmaceutical products, or negotiating, establishing and maintaining strategic relationships. Any growth of our company will require us to expand our management and our operational and financial systems and controls. If we are unable to do so, our business and financial condition would be materially harmed. If rapid growth occurs, it may strain our operational, managerial and financial resources.

We Will Depend On Third Parties To Manufacture And Market Our Products. We do not have, and do not now intend to develop facilities for the manufacture of any of our products for clinical or commercial production. Accordingly, we will need to develop relationships with manufacturers and enter into collaborative arrangements with licensees or have others manufacture our products on a contract basis. We expect to depend on such collaborators to supply us with products manufactured in compliance with standards imposed by the FDA and foreign regulators. In addition, we have no direct experience in marketing, sales or distribution, and we do not intend to develop a sales and marketing infrastructure to commercialize our pharmaceutical products. If we develop commercial products, we will need to rely on licensees, collaborators, joint venture partners or independent distributors to market and sell those products.

We Depend On Key Individuals To Develop Our Products And Pursue Collaborations. We are highly dependent on Dr. David Platt, President and Chief Executive Officer; Dr. Anatole Klyosov, a member of our Scientific Advisory Board and a consultant; and Dr. Eliezer Zomer, Vice President of Manufacturing and Product Development. The loss of any of these persons, or failure to attract or retain other key personnel, could prevent us from pursuing collaborations or developing our products and core technologies.

Risks Related to the Drug Development Industry

We Will Need Regulatory Approvals To Commercialize Our Products. We currently do not have products approved for sale in the U.S. or any foreign market. We are required to obtain approval from the FDA in order to sell our products in the U.S. and from foreign regulatory authorities in order to sell our products in other countries. The FDA s review and approval process is lengthy, expensive and uncertain. Extensive preclinical and clinical data and supporting information must be submitted to the FDA for each indication for each product candidate in order to secure FDA approval. The FDA could reject an application or require us to conduct additional clinical or other studies as part of the regulatory review process. Delays in obtaining or failure to obtain FDA approvals would prevent or delay the commercialization of our products, which would prevent, defer or decrease our receipt of revenues. If we receive initial regulatory approval, our product candidates will be subject to extensive and rigorous ongoing domestic and foreign government regulation.

Our Competitive Position Depends On Protection Of Our Intellectual Property. Development and protection of our intellectual property are critical to our business. If we do not adequately protect our intellectual property, competitors may be able to practice our technologies. Our success depends in part on our ability to obtain patent protection for our products or processes in the United States and other countries, protect

trade secrets, and prevent others from infringing on our proprietary rights.

Since patent applications in the United States are maintained in secrecy for at least portions of their pendency periods (published on U.S. patent issuance or, if earlier, 18 months from earliest filing date for most

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applications) and since other publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain that we are the first to make the inventions to be covered by our patent applications. The patent position of biopharmaceutical firms generally is highly uncertain and involves complex legal and factual questions. The U.S. Patent and Trademark Office has not established a consistent policy regarding the breadth of claims that it will allow in biotechnology patents.

We cannot assure you that all of our patent applications will issue as patents or that the claims of any issued patents will afford meaningful protection for our technologies or products. In addition, patents issued to us or our licensors may be challenged and subsequently narrowed, invalidated or circumvented. Patent litigation is widespread in the biotechnology industry and could harm our business. Litigation might be necessary to protect our patent position or to determine the scope and validity of third-party proprietary rights, and we may not have the required resources to pursue such litigation or to protect our patent rights.

Although we require our scientific and technical employees and consultants to enter into broad assignment of inventions agreements, we have not required Dr. Platt to do so. He has, however, assigned all his patents and patent applications of inventions related to our business. While our employees, consultants and corporate partners with access to proprietary information generally will be required to enter into confidentiality agreements, these agreements may not be honored.

Our Products Could Infringe The Intellectual Property Rights Of Others. We cannot assure that products based on our patents or intellectual property that we license from others will not be challenged by a third party claiming infringement of its proprietary rights. If we were not able to successfully defend our patents or licensed right, we may have to pay substantial damages, possibly including treble damages, for past infringement.

We Face Intense Competition In The Biotechnology And Pharmaceutical Industries. The biotechnology and pharmaceutical industries are intensely competitive. We face direct competition from U.S. and foreign companies focusing on drug delivery technologies which are rapidly evolving. Our competitors include major, multinational pharmaceutical and chemical companies, specialized biotechnology firms and universities and other research institutions. Many of these competitors have greater financial and other resources, larger research and development staffs and more effective marketing and manufacturing organizations, than we do. In addition, academic and government institutions are increasingly likely to enter into exclusive licensing agreements with commercial enterprises, including our competitors, to market commercial products based on technology developed at such institutions. Our competitors may succeed in developing or licensing technologies and products that are more effective or less costly than ours, or succeed in obtaining FDA or other regulatory approvals for product candidates before we do.

Health Care Cost Containment Initiatives And The Growth Of Managed Care May Limit Our Returns. Our ability to commercialize our products successfully will be affected by the ongoing efforts of governmental and third-party payors to contain the cost of health care. These entities are challenging prices of health care products and services, denying or limiting coverage and reimbursement amounts for new therapeutic products, and for FDA-approved products considered experimental or investigational, or which are used for disease indications without FDA marketing approval.

Even if we succeed in bringing any products to the market, they may not be considered cost-effective and third-party reimbursement might not be available or sufficient. If adequate third-party coverage is not available, we may not be able to maintain price levels sufficient to realize an appropriate return on our investment in research and product development. In addition, legislation and regulations affecting the pricing of pharmaceuticals may change in ways adverse to us before or after any of our proposed products are approved for marketing.

Our Insurance Coverage May Not Be Adequate In All Circumstances. In the future, we may, in the ordinary course of business, be subject to claims by, and liability to, persons alleging injury as a result of taking products we have under development. If we are successful in having products approved by the FDA, the sale of such products would expose us to additional potential product liability and other claims resulting from their use. This liability may result from claims made directly by consumers or by pharmaceutical companies or others

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selling such products. Although we currently have insurance coverage for both product liability and professional liability, it is possible that we will not be able to maintain such insurance on acceptable terms. Any inability to maintain insurance coverage on acceptable terms could prevent or limit the commercialization of any products we develop.

Risks Related to Our Stock

Stock Prices For Biopharmaceutical And Biotechnology Companies Are Volatile. The market price for securities of biopharmaceutical and biotechnology companies historically has been highly volatile, and the market from time to time has experienced significant price and volume fluctuations that are unrelated to the operating performance of such companies. Fluctuations in the trading price or liquidity of our common stock may adversely affect our ability to raise capital through future equity financings.

Trading of Our Shares Could Be Adversely Affected Because Our Stock Is Not Listed And Is A Penny Stock . Currently, our shares are traded on the OTC Bulletin Board (OTCBB) sponsored by the National Association of Securities Dealers. Trading volume in our shares is not consistent on a daily basis and our stockholders may be unable to sell their shares when they want or at a favorable price. We have not listed our stock and in the near term may not be able to meet the listing standards for any exchange or for the Nasdaq National Market or the Nasdaq SmallCap Market. Our stock is subject to SEC regulations that impose limitations upon the manner in which certain low priced equity securities, referred to as penny stocks are publicly traded. Under these regulations, a penny stock is defined as any equity security that has a market price of less than $5.00 per share, subject to certain exceptions for which we do not now qualify. Our stock does not regularly trade above $5.00 per share. Regulations require the delivery, prior to any transaction involving a penny stock, of a disclosure schedule explaining the penny stock market and the associated risks. They also require broker-dealers who recommend penny stocks to persons other than established customers and certain accredited investors to make a special written suitability determination for the purchaser and receive the purchaser s written agreement to a transaction prior to sale. These requirements make it more difficult to effect transactions in penny stocks as compared to other securities.

Four Principal Stockholders Own Enough Shares To Control The Company. Four of our principal stockholders, David Platt, James Czirr, Offer Binder and Anatole Klyosov own or control approximately 61% of our outstanding shares of our common stock, and Dr. Platt and Mr. Czirr together own approximately 49%. Some or all of these stockholders, acting in concert, will be able to continue to elect the Board of Directors and take other corporate actions requiring stockholder approval, such as recapitalization or other fundamental corporate action, as well as dictate the direction and policies of our company. Such concentration of ownership also could have the effect of delaying, deterring or preventing a change in control of the company that might otherwise be beneficial to stockholders.

Certain of our directors, officers or principal stockholders are offering for resale 615,846 shares of our common stock. This does not mean that any of these persons will sell all or any of such shares. None of such persons has a present intention to sell such shares and there currently are no agreements, arrangements or understandings with respect to the sale or distribution of any of the common stock by any of these directors, officers or principal stockholders. The sale of any or all of these shares by such persons or the perception that such sales will occur could materially adversely affect the market price of our common stock.

FORWARD-LOOKING STATEMENTS

This prospectus contains, in addition to historical information, forward-looking statements within the meaning of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements can be identified by the use of forward-looking terminology such as may, will, could, expect, anticipate, estimate, continue or other similar words. These forward-looking statements are based on management s c expectations and are subject to a number of factors and uncertainties which could cause actual results to differ materially from those described in

such statements. We caution investors that actual results

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or business conditions may differ materially from those projected or suggested in forward-looking statements as a result of various factors including, but not limited to, those described in the Risk Factors section of this prospectus. We cannot assure you that we have identified all the factors that create uncertainties. Readers should not place undue reliance on forward-looking statements. We undertake no obligation to publicly release the result of any revision of these forward-looking statements to reflect events or circumstances after the date they are made or to reflect the occurrence of unanticipated events.

USE OF PROCEEDS

We will not receive any of the proceeds from the sale of the shares owned by the selling security holders.

MARKET FOR OUR COMMON STOCK AND RELATED STOCKHOLDER MATTERS

Market for Our Common Stock

Our common stock trades under the symbol PROH on the Over-the-Counter Bulletin Board Electronic Quotation System maintained by the National Association of Securities Dealers, Inc. Our stock commenced trading on September 9, 2002. Approximately thirteen professional market makers hold themselves out as willing to make a market in our common stock. Following is information about the range of high and low bid prices for our common stock for each fiscal quarter since our stock commenced trading. These quotations reflect inter-dealer prices, without retail mark-up, mark-down or commission, and may not necessarily represent actual transactions.

Quarter Ended	High Bid Quotation	Low Bid Quotation
9/30/02	$ 4.00	$ 2.00
12/31/02	$ 3.34	$ 2.70
3/31/03	$ 3.14	$ 2.41
6/30/03	$ 5.00	$ 2.30

Equity Compensation Plans

On October 18, 2001, our Board of Directors adopted the Pro-Pharmaceuticals, Inc. 2001 Stock Incentive Plan which permits awards of incentive and non-qualified stock options and other forms of incentive compensation to employees and nonemployees such as directors and consultants. The Board reserved 2,000,000 of our shares of common stock for awards pursuant to the plan, all of which reserved shares could be awarded as incentive stock options. Our stockholders approved the plan on May 31, 2002.

The following table provides summary information on our equity incentive plans as of December 31, 2002:

	Equity Compensation Plan Information		
Plan category	Number of Securities To be Issued Upon Exercise of Outstanding Options, Warrants and Rights	Weighted-Average Exercise Price of Outstanding Options, Warrants and Rights	Number of Securities Remaining Available For Future Issuance Under Equity Compensation Plans (excluding securities reflected in column)
Equity compensation plans approved by security holders(1)	345,000	$ 3.50	1,655,000
Equity compensation plans not approved by security holders(2)	224,000	$ 3.50	N/A
Total	569,000		1,655,000

(1) The only compensation plan approved by stockholders is the Pro-Pharmaceuticals, Inc. 2001 Stock Incentive Plan.

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(2) During 2001, we entered into a consulting agreement with a non-employee, who was also a Board member and then a member of the Audit Committee, pursuant to which we granted 200,000 options to purchase common stock at an exercise price of $3.50 in consideration for services to be performed. A portion of these options vested during fiscal years 2001 and 2002, and the remainder will vest during 2003. In March 2002, we entered into a second agreement with the same non-employee, by which the Company granted 2,000 options a month to purchase common stock at an exercise price of $3.50 in consideration for monthly consulting services. On November 11, such agreement was superceded by an amendment, which was effective retroactively to the date of the original agreement, March 1, 2002. Under the amended agreement, we granted 24,000 options on March 1, 2002, which vest at a rate of 2,000 options per month, as services are performed.

Holders

As of May 31, 2003, there were 308 holders of record of our common stock, although we believe that there are additional beneficial owners of our common stock who own their shares in street name.

Dividends

There have been no cash dividends declared on our common stock since our company was formed. Dividends are declared at the sole discretion of our Board of Directors.

BUSINESS

Corporate Formation

We were incorporated as DTR-Med Pharma Corp. under Nevada law in January 2001 for the purpose of acquiring all the outstanding stock of our predecessor, Pro-Pharmaceuticals, Inc., which was a Massachusetts corporation engaged in a business we desired to acquire. From our incorporation until just before the acquisition, we were a wholly owned subsidiary of Developed Technology Resource, Inc., a Minnesota corporation whose common stock is publicly traded on the OTC Bulletin Board. In exchange for 1,221,890 shares of our common stock, Developed Technology transferred to us contractual rights. As part of that process, Developed Technology distributed its holdings of our common stock to its shareholders of record as of May 7, 2001. In anticipation of the acquisition of the Massachusetts company, we changed our name to Pro-Pharmaceuticals, Inc.

On May 15, 2001, we acquired all of the outstanding common stock of the Massachusetts corporation. We acquired these shares in exchange for 12,354,670 shares of our common stock. As a result, that corporation became our wholly owned subsidiary, and its shareholders through an exchange owned approximately 91% of the outstanding shares of our common stock, with the Developed Technology shareholders owning the remaining 9%. After the acquisition, we merged with the Massachusetts corporation and are the surviving corporation in the merger. The merger was treated as a capital transaction and was accounted for as a reverse merger in which Pro-Pharmaceuticals (Massachusetts) was the accounting acquirer.

Overview

We are a research and development pharmaceutical company that intends to identify, develop and seek regulatory approval of technology that will reduce toxicity and improve the efficacy of widely used chemotherapy drugs by combining the drugs with a number of specific carbohydrate compounds. Our fundamental objective is to increase the body s tolerance to the drugs by enabling delivery of the drugs while protecting healthy tissue. Our carbohydrate-based drug delivery system may also have applications for drugs now used to treat other diseases and chronic health conditions.

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In technical terms, we seek to reformulate existing cancer chemotherapy drugs with non-toxic carbohydrate-based compounds that are recognized by and adhere to specific binding sites on the surface of cancer cells. Reformulation of chemotherapy drugs already approved by the U.S. Food and Drug Administration has the following benefits for our business:

We expect fewer risks in drug development because our carbohydrate-based compounds would be combined with drugs already in widespread use. Use of carbohydrate compounds with increased capacity to bind to receptors only on cancer cells and combining the drug with a harmless carbohydrate polymer will reduce the toxic effect on healthy cells and permit better calibration (including possible increase) of dosages to diseased tissue.

We foresee a ready demand for chemotherapy drugs that are less toxic and have greater efficacy. We believe the pharmaceutical industry would respond favorably to drug delivery systems that upgrade existing chemotherapy treatments which patients could tolerate more easily. The industry would likely also be receptive to patent-protected drug delivery systems that attach to existing chemotherapy drugs whose patent protection has expired.

We believe that the development of drug delivery systems to upgrade these widely used drugs can be accomplished with much less investment compared to the typical expenditures made by large pharmaceutical companies for a new drug launch.

Our Business Strategy and Initial Objective

The initial objectives of our business strategy are as follows:

Verify and extend the carbohydrate-based drug enhancement concept utilizing our approach for developing novel cancer chemotherapy products.

Expand and enhance clinical applications of at least five widely used chemotherapy drugs (5-Fluorouracil, Adriamycin®, Taxol®, Cytoxan®, and Cisplatin®) by combining them with our carbohydrate-based drug delivery system.

Demonstrate the safety and efficacy of such product candidates by means of preclinical evaluation and submitting investigational new drug (IND) applications to the FDA.

Accelerate commercialization by identifying products that qualify for fast-track designation by the FDA (further described below) with respect to products to be used in treatment of types and stages of cancer for which treatments are now inadequate.

Leverage our carbohydrate-based drug enhancement technology by applying it to other FDA-approved drugs, including drugs for conditions or ailments other than cancer, that would benefit from reduced toxicity and/or greater efficacy. This strategy would enable us to increase the portfolio of drugs to which our technology may be applied without corresponding development risk and expense of creating new drugs.

Apply our drug enhancement system with the aim of extending the patent life of current drugs, or as to drugs with expired patents, thus creating new patent protection.

Limitations of Chemotherapy for Cancer Treatment

Cancer is a disease characterized by uncontrolled growth and spread of abnormal cells. The disease may be caused by patient-specific factors such as genetic predisposition, immune deficiency, hormones, diet and smoking, or external factors such as exposure to a toxic environment. It is a leading cause of death in the United States and worldwide.

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The most widely used methods to treat cancer are surgery, radiation and chemotherapy. Cancer patients often receive a combination of these treatments, and about half of all patients receive chemotherapy. Both radiation and chemotherapy have significant limitations that often result in treatment failure. In the case of chemotherapy, these limitations include:

Toxicity. Most chemotherapy agents kill cancer cells by disrupting the cell division process. Cells are killed once they begin to undergo division and replication. Although these agents are effective on cancer cells, which generally grow rapidly through cell division, they also kill healthy non-cancerous cells as these cells undergo ordinary division. This is particularly apparent in fast-growing normal cells, such as blood cells forming bone marrow, in the digestive tract, hair follicles, and reproductive organ cells. As the chemotherapy harms healthy tissue, the effectiveness of the drug is limited because dosage levels and treatment frequency cannot exceed tolerance levels for noncancerous cells. Moreover, the chemotherapy regimen often dramatically diminishes the quality of a patient s life through its physical and emotional side effects.

Inability to Selectively Target Diseased Cells. The administration of chemotherapy occurs in such a way that the drug reaches both healthy and diseased tissue. Normal cells are generally as receptive as tumors to the toxic effects of chemotherapy. Without the ability to target the drug exclusively to cancerous tissue, chemotherapy dosages must be kept within a range that healthy tissue can tolerate, thus reducing the optimal effectiveness of chemotherapy on diseased tissue.

Drug Delivery Technologies

General

The ultimate objective of enhanced drug delivery is to control and optimize the localized release of a drug at the target site and rapidly eliminate from the body the portion of the drug that was not delivered to the diseased tissue. Conventional drug delivery systems such as controlled release, sustained release, transdermal systems, and others are based on a physical erosion process for delivering active product into the systemic circulation over time with the objective of improving compliance by patients with a therapy regimen. These systems do not address the biologically important issues such as site targeting, localized release and elimination of undelivered drug from the body. The major factors that impact the achievement of this ultimate goal are:

Physical characteristics of a drug. These characteristics affect, among other things, the drug s interactions with the intended pharmacological target sites and undesired areas of toxicity; and

Biological characteristics of the diseased area. These characteristics impact the ability of a drug to selectively interact with the intended target site to allow the drug to express the desired pharmacological activity.

Both of these factors are important in increasing efficacy and reducing toxicity of cancer drugs. Biotechnology affords a new opportunity in drug delivery techniques by taking advantage of biological mechanisms such as drug-cell recognition and interactions, and particular physical characteristics of cancerous tissue.

Our Focus: Carbohydrate-Based Drug Enhancement Technology

We are attempting to develop a carbohydrate-based drug delivery technology to direct cancer drugs more selectively to tumor tissue so as to reduce the toxic side effects and improve the tumor reduction capacity of chemotherapy drugs now in use. Carbohydrates are found in the structural elements of cell walls and, among other functions, serve as recognition elements in biomolecules, enabling molecule-cell recognition, and hence, molecular targeting. The dense concentration of chemical functional groups within carbohydrates compared to other chemicals suits them for use in cell recognition applications in biological systems.

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Our drug enhancement technology is intended to take advantage of the following biological mechanisms to improve drug delivery:

- Disease-specific carbohydrate recognition; and
- Enhanced permeability and retention in tumors.

Our technology does not change the chemistry of the drugs themselves, but rather attaches cancer drugs to proprietary carbohydrate compounds, which interact with sugar-specific proteins on the surface of the tumor cell. Because of these cell surface interactions, we believe that these compounds will increase cell permeability, resulting in increased targeted absorption of drugs by cancer cells. These cell surface interactions may also reduce the cells ability to adhere to each other as well as to normal tissue, resulting in diminished ability of cancer cells to metastasize, or spread to other tissue systems.

Initial Chemotherapy Applications

We believe that our carbohydrate-based drug enhancement technology applies to essentially any oncology drug whose delivery to the target can be improved by utilizing sugar-specific recognition at the cancer cell surface. Our initial program is designed to be risk-contained in that it will focus on proven drugs for which there are already a great deal of data on their therapeutic efficacy and toxicity, along with an accumulated knowledge of their limitations. We intend to apply our drug delivery technology initially to five widely used chemotherapy agents: 5-Fluorouracil, Adriamycin®, Taxol®, Cytoxan® and Cisplatin®. Each of these drugs is among the most popular drugs used in cancer chemotherapy treatment in the United States, and for each of these drugs there is a strong need for improving its therapeutic efficacy and decreasing its toxicity.

5-Fluorouracil (5-FU) is a fluorinated pyrimidine (a nucleic acid component). It interferes with the synthesis of DNA and inhibits the formation of RNA. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU provokes unbalanced growth and death of the cell. The effect of DNA and RNA deprivation is most marked on those cells which grow more rapidly and which take up the 5-FU at a more rapid rate, such as cancer cells. 5-FU is effective against cancers of the colon, rectum, breast, stomach and pancreas. This drug is also toxic, resulting in side effects such as nausea, vomiting, mouth sores, gastrointestinal ulceration and bleeding, loss of hair, skin darkening and fatigue. 5-FU is manufactured by Roche Laboratories for intravenous administration. Originally patented in the late 1950s, its patent protection has expired.

Adriamycin® (generic name: doxorubicin hydrochloride) is a cytotoxic agent that selectively kills malignant cells and causes tumor regression. It binds to the DNA, and presumably inhibits nucleic acid synthesis. It is used to treat, among others, leukemia, cancers of the breast, ovaries, bladder, stomach and thyroid, as well as Hodgkin s and non-Hodgkin s lymphoma. Adriamycin® is toxic, resulting in side effects such as nausea, vomiting, loss of hair, mouth sores, colon ulceration and heart damage. It is manufactured by Pharmacia Upjohn for intravenous administration. Originally patented in 1971, its patent protection has expired.

Taxol® (generic name: paclitaxel) is a relatively new anti-leukemic and anti-tumor agent, possessing a cytotoxic activity. It suppresses cell division by binding to so-called microtubules that form in a cell s nucleus to help move the chromosomes around during the division process. Taxol® is most effective against ovarian and advanced breast cancers, particularly after failure of standard chemotherapy. Studies indicate that it might be effective against leukemia, lung carcinoma, colon carcinoma, renal carcinoma, melanoma, and CNS carcinoma. Taxol® is toxic, and patients receiving it often develop problems ranging from rashes, drop in blood pressure and anemia to major breathing problems, hives and/or fluid buildup around the heart and bone marrow suppression. Almost all patients experience hair loss from Taxol®, and some patients experience severe hypersensitivity reactions to Taxol®. It is manufactured by Bristol-Myers-Squibb Company for intravenous administration. We believe that there are no patents covering the

composition of Taxol (paclitaxel).

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Cytoxan® (generic name: cyclophosphamide) has action leading to cross-linking of RNA of tumor cells, and thereby interferes with the growth of susceptible rapidly proliferating malignant cells. It is effective against a range of cancers, such as malignant lymphomas, Hodgkin s disease, various leukemias, and cancer of the breast and ovaries. This drug is toxic, with side effects including nausea, vomiting, anorexia, diarrhea, skin rash and darkening and, in extreme cases, heart damage or failure, and secondary malignancies. It is manufactured by Bristol-Myers-Squibb Company for intravenous and oral administration. We believe that there are no patents covering the composition of Cytoxan® (cyclophosphamide).

Cisplatin® appears to act by inhibiting DNA synthesis. It is effective against metastatic testicular and ovarian tumors (typically in combination with other chemotherapeutic agents, such as Cytoxan, above), and advanced bladder cancer. This drug is toxic, with side effects including renal toxicity, nausea, vomiting, anorexia, diarrhea and anemia. It is manufactured as PLATINOL® by Bristol-Myers-Squibb Company for intravenous injection. We believe that there are no patents covering the composition of Cisplatin®.

Preclinical Studies

Toxicity Studies

Our initial toxicity studies in smaller animals, conducted in early 2001, were performed to test the potential reduction of toxicity of anticancer drugs in combination with certain of our polysaccharide compounds. The results of one study demonstrated that one of our polysaccharide compounds, DAVANAT™, might significantly decrease the toxicity of 5-FU. A second, similar study was performed to test a potential reduction of toxicity of Adriamycin in combination with each of two selected polysaccharide compounds. The results indicated that DAVANAT™ might decrease the toxicity of Adriamycin®. The fact that two different cancer drugs with chemically unrelated structures showed a marked reduction of their toxicity in combination with DAVANAT™ indicates that there might be some fundamental underlying biological reasons related to this polysaccharide, rather than to the drugs, for the reduction in toxicity.

In subsequent pre-clinical experiments conducted in 2001 and 2002, we studied on larger animals the toxicity reduction of DAVANAT™-1, a DAVANAT™ combination with 5-FU/leocovorin, which had demonstrated toxicity reduction in the prior studies. These experiments were performed in accordance with FDA guidelines and recommendations on rats (acute and long-term toxicity study) and dogs (acute and long-term toxicity study) measuring the effect of the DAVANAT™/5-FU combination on body weight, feed consumption, blood structure and survival of these animals. Preliminary results indicate that the DAVANAT™/5-FU combination decreased toxicity, resulting in lower animal mortality and decreased loss of blood structure components in comparison to the results in animals which were administered 5-FU/leocovorin alone. These studies were presented to the FDA as part of our IND submission (detail below). We conducted additional toxicity studies on rats using escalating dosages of DAVANAT™ and submitted these results to the FDA in an amendment to our IND in support of our Phase I clinical trials. The results of these additional toxicity studies were such that the FDA approved our commencement of Phase I clinical trials.

Efficacy Studies

We undertook independent studies at Southern Research Institute and Charles River Laboratories to test a potential change in the therapeutic efficacy of the DAVANAT™ /5-FU combination that had decreased toxicity of the drug in healthy animals. Results of the studies demonstrated that DAVANAT™ might also increase efficacy of 5-FU when administered into cancer-carrying animals. The studies, conducted with two different human colon tumors implanted into the test animals, demonstrated a decrease in tumor size following administration of 5-FU/leocovorin alone, as well as a significant decrease with the administration of the DAVANAT™/5-FU combination.

Two of our efficacy studies were conducted to evaluate the compatibility of DAVANAT™ with leucovorin, which is commonly used in cancer treatment with 5-FU. The studies showed that DAVANAT™ and leucovorin

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do not interfere with each other when administered following standard procedure, and that the DAVANAT™/5-FU combination is superior, compared to 5-FU/leucovorin when both are administered in tumor-bearing animals. Leucovorin is a folinic acid derivative, which may enhance both the therapeutic and toxic effect of 5-FU in cancer therapy. In these studies, the growth of the tumor was decreased significantly by using a DAVANAT™/5-FU combination compared to a 5-FU/leucovorin combination.

We also conducted a study that involved injecting radiolabeled DAVANAT™ (with and without 5-FU) into tumor-free and tumor-bearing animals. The study provided experimental data with respect to DAVANAT™ distribution in organs and tissues (liver, kidney, lungs, plasma, and tumor) and the capacity of such organs and tissue to clear DAVANAT™ after various time periods. The study suggested that DAVANAT™ may protect the liver from the toxic effect of 5-FU yet increase the amount, and hence the therapeutic effect, of 5-FU in the tumor. In other words, we have indications that DAVANAT™ may decrease toxicity and increase efficacy of 5-FU.

In addition to the DAVANAT™-1/5-FU combination, we are also conducting pre-clinical studies for doxurubicin and paclitaxel, both in combination with DAVANAT™ and other polysaccharide compounds.

Although the foregoing studies are encouraging, the results achieved in preclinical studies with animals are often not duplicated in human patients. Please see Risk Factors We Have Only Recently Began Clinical Trials And Results Are Uncertain.

Phase I Clinical Trials

We submitted an IND to the FDA on May 26, 2002 based on the pre-clinical data obtained from our 5-FU studies. The FDA accepted the IND as of June 26, 2002 which authorized us to begin Phase I clinical trials with humans. We filed an amendment to the IND on November 27, 2002 in order to incorporate new toxicology data and to enable us to undertake dose escalation in our Phase I trials. In response to the amendment, the FDA approved the dose escalation schema which would allow assessment in clinical trials of DAVANAT™ doses anticipated to be in the range of those for which the pre-clinical studies suggested efficacy.

In Phase I we are evaluating the ability of cancer patients to tolerate increasing doses of DAVANAT™ while receiving a stable dose of 5-FU for treatment of a variety of solid tumors which have not responded to accepted therapies. The Phase I study has two primary objectives: (1) to determine the maximum dose of DAVANAT™ that can be tolerated when administered with a stable dose of 5-FU, and (2) to define the dose-limiting toxicities of DAVANAT™ in combination with 5-FU. We expect that up to 40 male and female patients suffering from advanced solid malignancies, who failed the accepted chemotherapeutic, radiation, and/or surgical treatments, will participate in the study.

We have identified four clinical sites and lead investigators in which to undertake our Phase I trials. On February 10, 2003, we dosed the first patients at a private oncology treatment center in Howell, New Jersey. On May 14, 2003, we announced the dosing of a patient at the Ochsner Cancer Institute in New Orleans. Additionally, on June 24, 2003, we announced the dosing of a patient at the Norris Cotton Cancer Center at Dartmouth-Hitchcock Medical Center in Lebanon, NH.

We have also engaged a professional consultant, Dr. Marilyn Pike, who is affiliated with Harvard Medical School and Massachusetts General Hospital, to serve as Medical Director of our clinical trials.

The pharmaceutical company with which we contracted to produce DAVANAT™, a certified GMP facility, has manufactured sufficient quantities for the doses that will be needed for the human clinical trials.

We have engaged PRA International Inc. to serve as our independent Contract Research Organization (CRO) to manage and implement the clinical trials on our behalf, and Medidata Solutions Inc. to construct an

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on-line electronic data capture (EDC) method to collect and aggregate the clinical trial data. We expect that this will better enable us to manage clinical data and increase the speed at which such data is reported and compiled. We believe this may accelerate our commencement of Phase II clinical trials.

Other Carbohydrate-Cancer Drug Formulations

We have chemically synthesized four novel products that are carbohydrate derivatives of Adriamycin®, and have conducted preclinical studies in mice of both toxicity (effects on healthy animals) and efficacy (on cancer-carrying animals). Preliminary results of these experiments indicate that all four of the synthesized carbohydrate-Adriamycin