

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

GTC BIOTHERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Massachusetts

(State or other jurisdiction of
incorporation or organization)

04-3186494

(I.R.S. Employer
Identification Number)

**175 Crossing Boulevard
Framingham, Massachusetts 01702
(508) 620-9700**

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Geoffrey F. Cox
Chairman, President and Chief Executive Officer
GTC BIOTHERAPEUTICS, INC.
175 Crossing Boulevard
Framingham, Massachusetts 01702
(508) 620-9700**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

with copies to:

**Nathaniel S. Gardiner, Esq.
Palmer & Dodge LLP
111 Huntington Avenue
Boston, Massachusetts 02199
(617) 239-0100**

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.

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	Proposed maximum aggregate offering price(1)	Amount of registration fee
Common Stock, \$0.01 par value(2)	\$40,000,000	\$3,236.00

- (1) Estimated solely for the purpose of determining the registration fee and computed pursuant to Rule 457(o) under the Securities Act of 1933, as amended (the "Securities Act"). This Registration Statement registers an indeterminate number of shares of common stock that the registrant may sell from time to time. The aggregate offering price for all the shares of common stock that the registrant may sell from time to time pursuant to this Registration Statement will not exceed \$40,000,000.
- (2) Includes associated preferred stock purchase rights issuable pursuant to the registrant's Shareholder Rights Agreement dated as of May 31, 2001, which rights, prior to the occurrence of certain events, will not be exercisable or evidenced separately from the common stock.

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 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

The information in this prospectus is not complete and may be changed. We 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 we are not soliciting offers to buy these securities in any state where the offer or sale is not permitted.

Preliminary Prospectus

Subject to Completion, dated December 23, 2003

\$40,000,000
GTC Biotherapeutics, Inc.
Common Stock

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission using a “shelf” registration process. Under the shelf registration process, we may from time to time issue and sell to the public shares of our common stock in one or more offerings. We may sell common stock directly to investors or through agents, underwriters or dealers. Each time we sell common stock we will provide specific terms of the offering in a supplement to this prospectus. The prospectus supplement may also add, update or change information contained in this prospectus. You should read this prospectus and the applicable prospectus supplement carefully before you invest in our common stock. This prospectus may not be used to consummate a sale of common stock unless accompanied by the applicable prospectus supplement.

The aggregate offering price of all common stock sold under this prospectus will not exceed \$40,000,000.

Our common stock is quoted on The NASDAQ National Market under the symbol “GTCB.” On December 22, 2003, the last reported sale price for the common stock was \$2.98 per share.

Investing in our common stock involves a high degree of risk. See “Risk Factors” on page 3 for a discussion of some important risks you should consider before buying any shares of our common stock.

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

The date of this prospectus is

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THE COMPANY

We are a leader in the development, production and commercialization of therapeutic proteins in the milk of animals. Using a process known as transgenics, we insert protein-specific DNA into the animal enabling it to produce that specific protein in its milk. Our efforts are focused on the development of such proteins for therapeutic use because we believe that transgenic production offers significant economic and technological advantages over traditional protein production systems. Our technology is well suited to developing both large-volume protein therapeutics as well as products that are difficult to produce in significant quantities from conventional production systems. We have more than a dozen programs in development, including internal proprietary products. We have completed enrollment in a clinical efficacy study in Europe with our lead program, recombinant human antithrombin III, a human blood plasma protein being developed under the name ATryn®. We expect to file for marketing authorization of ATryn® in Europe by February 2004. In our other internal programs, we are developing a recombinant human serum albumin and a malaria vaccine. Our external program collaborations are developing transgenic versions of products such as monoclonal antibodies and immunoglobulin fusion proteins for conditions such as rheumatoid arthritis, HIV/AIDS, cancer and other autoimmune conditions. We generally pursue negotiations of commercial partnership agreements for supply of these products. These agreements are typically established following the development of initial data, such as characterization of the product in preclinical testing or clinical studies.

Our principal executive offices are located at 175 Crossing Boulevard, Framingham, Massachusetts 01702, and our telephone number is (508) 620-9700.

RISK FACTORS

You should carefully consider the risks described below in evaluating us, our business and any investment in our common stock. Additional risks not presently known to us may also impair our business operations. If any of the following risks actually occur, our business, financial condition or results of operations would likely suffer and the trading price of our common stock could decline which means you may lose all or part of your investment.

We expect to incur future operating losses and may never become profitable.

We have had operating losses since our inception, and we expect losses to continue for the next several years. From our inception in 1993 to September 28, 2003, we have incurred cumulative losses of approximately \$142 million. Our net losses for fiscal years ended 2000, 2001 and 2002, and for the interim period ended September 28, 2003, have been \$14.2 million, \$16.6 million, \$24.3 million, and \$21 million, respectively. These losses have resulted principally from the costs of our research and development activities and losses from our discontinued operations. We expect to continue incurring significant operating losses for at least the next several years as we incur increased costs and expenses associated with clinical trials and submissions for regulatory approvals. We may never receive material revenues from product sales or become profitable.

We depend on collaboration agreements for our current revenue.

Our revenues and business strategy depend largely on our entering into additional transgenic development agreements with third parties, even in the case of development programs for our own therapeutic compounds. We may not be able to establish these agreements on commercially acceptable terms, if at all, depending on the market position of our technology. The willingness of potential collaborators depends on factors such as the perceived technological or economic advantages of transgenic production and our ability to structure a mutually acceptable collaboration arrangement. In the case of our own programs for development of proteins proprietary to us, known as internal programs, the attractiveness of the program's commercial potential or other advantages the program

offers the partner will also affect our ability to obtain collaborators. Even if we enter into transgenic development agreements, the collaborations may ultimately be unsuccessful, our partners could terminate the agreements or the agreements could expire before meaningful developmental milestones are reached. The failure of any significant number of these collaborations could have a material adverse effect on our business.

The majority of our collaborations are, and will likely continue to be, external programs that involve proteins proprietary to our partners. Much of the revenue that we may receive under these collaborations will depend upon our partners' willingness and ability to successfully develop and commercially introduce, market and sell the version of the collaborator's product derived from our transgenic production systems in goats and other mammals. Our partners may develop competitive production technologies or competitive products outside of their collaborations with us, which could have a material adverse effect on our business.

To date, the scope of our collaboration agreements have generally been limited to transgenically producing quantities of targeted proteins. These initial development projects may not successfully produce the desired protein quantities or lead to collaboration agreements to commercially produce any proteins. The success of any collaboration ultimately will be dependent upon our collaborator deciding to seek regulatory approval and to market our transgenically produced version of their product or to invest in a transgenic product that we have developed. Depending upon the terms of any future collaborations, our role in the collaboration will often be limited to the production aspects of the proteins. As a result, we may also be dependent on collaborators for other aspects of the development of any transgenic product, including preclinical and clinical testing and regulatory approval, and marketing and distribution of any transgenic product.

We face uncertainty in raising additional funds for our operations.

In order to develop and bring our transgenic products to market, we and our collaboration partners must commit substantial resources to costly and time consuming research, preclinical testing and clinical trials. As of November 2, 2003, we had \$5.5 million in cash and cash equivalents and \$25.6 million in marketable securities, which were offset in part by our \$8.4 million in current liabilities. We expect our current cash resources and partnering revenue opportunities will be sufficient to fund operations into 2005. Our projected revenue and cash use depends upon attracting additional partnering revenues from existing and additional collaborations. If we do not substantially achieve our revenue projections, we could be forced to delay, scale back or eliminate one or more of our research and development programs.

Our cash requirements may vary materially from those now planned, depending upon the results of research and development, competitive and technological advances, the terms of future collaborations, regulatory requirements and other factors. If our business does not become profitable before we exhaust existing resources, we will need to obtain additional financing, through public or private sources, including debt or equity financing, or through collaborative or other arrangements with corporate partners. Depending on the state of the capital markets, interest rates, our financial profile and other factors at that time, we may not be able to obtain adequate funds on acceptable terms when needed. If we raise capital through the sale of equity, or securities convertible into equity, existing stockholders' proportionate ownership in us will be diluted. If we cannot obtain financing, we could be forced to delay, scale back or eliminate some of our research and development programs.

Transgenic technology is in a relatively early stage.

Developing products based on transgenic technology is subject to significant technological risks. Most of our transgenic protein products are in the early development stage. Each DNA construct is unique and it is possible that it might not be expressed in the transgenic animal's milk at a level that is

commercially viable. Purifying the recombinant protein out of the milk to use as a biotherapeutic may be too difficult to be commercially feasible. In addition, production of the recombinant protein may have negative effects on the health of either the mammary gland or more systematically on the animal as a whole. This would compromise the ability of the animal to produce the recombinant protein. Directing the mammary gland to produce additional proteins in the milk could negatively effect lactation, thereby shutting down milk production. The mammary gland may also modify a protein in such a manner that it is non-functional or harmful to human subjects. It is also possible that there may be disease agents present in goats or cows that would prevent the use of products derived from these animals. If an as yet unknown disease was identified in these animals and government agencies banned the use of animal products, recombinant proteins from milk could not be used.

To our knowledge, no other entity has completed human clinical trials necessary to receive marketing authorization for any protein produced in the milk of transgenic animals and until European regulatory authorities approve our planned application for marketing authorization of ATryn® in Europe, we will not have confirmation that our ATryn® trials are sufficient for approval in Europe. If we are unable to complete all clinical trials that may be required, or if a transgenically produced protein is not proved to be safe or effective, it would have a material adverse effect on our business and operations. In addition, it is possible that research and discoveries by others could render our transgenic technology obsolete or noncompetitive as a method of production for protein-based therapeutic products.

If clinical trials of any of our transgenic product candidates are unsuccessful or delayed, we would be unable to meet our anticipated development timeline, which could cause our stock price to decline.

We and our collaborators must demonstrate through preclinical and clinical trials that our transgenic product candidates are safe and effective for use in humans. Clinical trials are expensive and may take several years. Several factors could prevent or delay completion of these trials, including an inability to enroll the required number of patients or demonstrate adequately the safety or efficacy of the product for humans. If safety concerns develop, regulatory authorities could stop our trials. Furthermore, the results from early clinical trials are often not predictive of results in later clinical trials.

We cannot market and sell our transgenic products in the United States or in other countries if we fail to obtain the necessary regulatory approvals.

Before we can sell any transgenically produced drug or biological products that we or our collaborators develop, we must receive regulatory approvals by federal, state and local governmental authorities, including the United States Food and Drug Administration, or FDA, and similar agencies in other countries. To date, none of our transgenically produced products have been approved for sale in the United States or any foreign country. Moreover, to our knowledge, no protein produced in the milk of a transgenic animal has reached the stage in the regulatory process that would allow it to be submitted to the FDA, or any other regulatory agency, for final regulatory approval. Obtaining required regulatory approvals for our transgenically produced products may take several years to complete and is expensive and uncertain. It is possible that the FDA or any other regulatory authority may not act quickly or favorably on our requests for approval or will require us to provide additional data that we do not currently anticipate. For example, the FDA may impose restrictions and demands on our clinical trials that require additional resources and result in longer delays than we anticipate. In addition, the FDA may require us to conduct further clinical trials and post-marketing testing and surveillance to monitor the effects of approved products. The FDA or other regulatory authorities may also place conditions on approval that could restrict the commercial applications of such products.

Failure to comply with extensive FDA or similar regulations may result in delay, suspension or cancellation of a trial or a regulatory authority's refusal to accept test results. Regulatory authorities

may have varying interpretations of our pre-clinical and clinical trial data, which could delay, limit or prevent regulatory approval or clearance. Because transgenic products represent novel therapeutic products, the process for regulatory approval is unproven. There may be additional delays in regulatory approval due to issues arising from the breeding of transgenic animals and the use of proteins derived from them. Any delays or difficulties in obtaining regulatory approval or clearance for transgenically produced products may:

- adversely affect the marketing of any transgenic products we or our collaborators develop;
- impose significant additional costs on us or our collaborators;
- diminish any competitive advantages that we or our collaborators may attain; and
- limit our ability to receive royalties and generate revenue and profits.

If we do not receive regulatory approvals for our transgenically produced products in a timely manner, we will not be able to commercialize our products, or their commercialization may be limited or delayed and, therefore, our business and stock price will suffer.

Even if we receive regulatory approval for our transgenically produced products, the FDA or similar agencies in other countries may impose limitations on the indicated uses for which our products may be marketed. These limitations could reduce the size of the potential market for a product. Failure to comply with applicable FDA and other regulatory requirements can result in, among other things, warning letters, fines, injunctions, civil penalties, recall or seizure of products, total or partial suspension of production, refusal of the government to renew our marketing applications and criminal prosecution.

We are in discussions with the FDA regarding our clinical and regulatory strategy for approval of ATryn® in the United States. In response to an investigational new drug application, or IND, filed with the FDA in 2003 for clinical development of ATryn® in the hereditary deficiency indication, the FDA has provided us guidance that it wishes to see a controlled study as a basis for approval, which may not be feasible for this indication. Such a study has not been required under the advice we have received from the European regulatory authority for approval of ATryn® in the hereditary deficiency indication in Europe. We are in a continuing dialogue with the FDA to define an appropriate clinical and regulatory strategy for ATryn® approval in hereditary deficiency or another indication that meets the agency's requirements. We intend to move forward with our clinical development program for ATryn® in the United States in 2004 under an appropriate IND once agreement has been reached with the FDA. Until we know the nature of any clinical program that may be agreed with the FDA, we are unable to estimate a timetable for filing a Biologics License Application on ATryn® in the United States. If we do not reach agreement with the FDA on an appropriate IND for ATryn®, we will not be able to proceed with its clinical development in the United States.

Any transgenic products for which we obtain regulatory approval will be subject to continuing review and extensive regulatory requirements, which could affect their manufacture and marketing.

If and when the FDA or other foreign agencies approve any of our transgenic products under development, the manufacture and marketing of these products will be subject to continuing regulation and product approvals may be withdrawn if problems occur after initial approval. Post-approval regulation includes compliance with current Quality Systems Regulations and Good Manufacturing Practices, known as QSR/GMP, adverse event reporting requirements and prohibitions on promoting a product for unapproved uses. We will also be required to obtain additional approvals for any significant alterations in the product's labeling or manufacturing process. Enforcement actions resulting from failure to comply with QSR/GMP requirements could result in fines, suspensions of approvals, recalls of products, operating restrictions and criminal prosecutions, and affect the manufacture and marketing of our transgenic products. The FDA or other regulatory agencies could withdraw a previously

approved product from the market upon receipt of newly discovered information, including a failure to comply with regulatory requirements and the occurrence of unanticipated problems with products following approval. Any of these withdrawals could adversely affect our operating results.

We have limited manufacturing capability and may rely on third party contract manufacturers to purify and formulate our transgenic products.

We have the capability to purify pre-clinical and clinical trial quantities of our transgenic product candidates. Our current capacity allows us to purify products for clinical trials, up to and including phase II. We also rely upon third party manufacturers to purify and formulate significant pre-clinical and clinical quantities of our transgenic product candidates from the milk of our transgenic animals. We will depend on these third party manufacturers to perform their obligations in a timely manner and in accordance with applicable government regulations in order to conduct our clinical trials or commercialize any of our products. In addition, there are very few third party manufacturers that have sufficient production capacity to manufacture all of our product candidates either for our clinical trials or on a commercial scale. Our third party manufacturers may encounter difficulties, including problems involving:

- inconsistent production yields;
- poor quality control and assurance or inadequate process controls; and
- lack of compliance with FDA and other regulations.

These contract manufacturers may not be able to manufacture our product candidates at a cost or in quantities necessary to make them commercially viable. If we are unable to enter into agreements with additional manufacturers on commercially reasonable terms, or if there is poor performance on the part of our third party manufacturers, we may not be able to complete development of, or market, our transgenic product candidates.

We have entered into a contract with Cambrex Bio Science MA, Inc. for the large scale purification of our lead product candidate, ATryn®. We have a five year, renewable supply agreement with Cambrex, which will expire in 2007 if not renewed. Although we have identified possible alternative suppliers with respect to the purification of this product, interruptions in these services and the process of changing to an alternative manufacturer could have a material adverse effect on our timely ability to manufacture bulk delivery of ATryn® for delivery to our collaborators.

Transgenic products may never become commercially successful.

Even if our transgenically produced products are successfully developed and approved by the FDA and foreign regulatory agencies, they may not enjoy commercial acceptance or success, which would adversely affect our business and results of operations. Several factors could limit our success, including:

- limited market acceptance among patients, physicians, medical centers and third party payors;
- our inability to access a sales force capable of marketing the product;
- our inability to supply a sufficient amount of product to meet market demand;
- the number and relative efficacy of competitive products that may subsequently enter the market; and
- for a transgenic product designed to replace or supplement currently marketed non-transgenic products, the relative risk-benefit profile and cost-effectiveness of the transgenically produced product.

In addition, it is possible that we or our collaborative partners will be unsuccessful in developing, marketing or implementing a commercialization strategy for any transgenic products.

Our business may fail due to intense competition in our industry.

The industries in which we operate are highly competitive and may become even more so. Some of our competitors have greater financial and human resources and more experience in research and development than we have. We will need to continue to devote substantial efforts and expense in research and development to maintain a competitive position for our transgenic production technology and potential product offerings. It is also possible that others will develop alternative technologies or products that will render our proposed products or technologies obsolete. We may encounter significant competition for our protein development and production contracts from other companies. In addition, our potential transgenic production capabilities may face significant competition from biological products manufactured in cell culture or by other traditional protein production methods. Our business will also compete against other companies whose business is dedicated to offering transgenic production and with prospective customers or collaborators who decide to pursue such transgenic production internally. Competitors that complete clinical trials, obtain regulatory approvals and begin commercial sales of their products before us will enjoy a significant competitive advantage. We anticipate that we will face increased competition in the future as new companies enter the market and alternative technologies become available.

Two other companies known to GTC are extensively engaged in the application of transgenic technology in mammals for the production of proteins for therapeutic use in humans: Pharming Group N.V. and PPL Therapeutics plc. Pharming, based in the Netherlands, is primarily engaged in the development of recombinant proteins in the milk of transgenic cows and rabbits. Pharming has two products in clinical development that are in phase II studies. PPL, based in Scotland, utilizes primarily sheep for transgenic protein production. PPL has developed recombinant alpha-1 antitrypsin into phase II stage of clinical testing. There are also other companies seeking to develop transgenic technology in animals and in plants, which may be competitive with our technology with respect to our patents and proprietary rights as discussed further below.

For ATryn[®], a number of companies internationally produce and market antithrombin from the fractionation of human plasma. Aventis has approximately a 40% share of this market worldwide. Bayer is the only company that has commercially available fractionated antithrombin material that is approved for sale in the U.S., which sales represent only about 1% of the worldwide market.

There are a number of companies worldwide that produce and market human serum albumin from the fractionation of human plasma. We estimate that Bayer and Aventis sales represent approximately a 30% and 10% share, respectively, of the worldwide market for human serum albumin. We are aware of two companies internationally that are developing recombinant forms of human serum albumin derived from yeast cultures. One company, Aventis, is developing its recombinant albumin product for the excipient market.

We may face public concerns about genetic engineering in animals.

Our activities involve genetic engineering in animals. The commercial success of our potential products will depend in part on public acceptance of the use of genetic engineering. Public attitudes may be influenced by claims that these types of activities are unsafe and our products may not gain the acceptance of the public or the medical community. Negative public reaction to genetic engineering activities in general could result in greater restrictive legislation and regulations involving nuclear transfer and other methodologies which could impede our ability to conduct efficiently our business, delay preclinical studies or future clinical trials, or prevent us or our partners from obtaining regulatory approvals or commercializing transgenically produced products.

We depend on patents and proprietary rights that may fail to protect our business.

Our success will partly depend on our ability to obtain and maintain patent or other proprietary protection for our technologies, products and processes such as:

- compositions of matter or processes;
- processes developed by our employees; or
- uses of compositions of matter discovered through our technology.

We may not be able to obtain the necessary protection. Our success will also depend on our ability to operate without infringing the proprietary rights of other parties. Legal standards relating to the validity of patents covering pharmaceutical and biotechnological inventions and the scope of claims made under these patents are still developing. There is no consistent policy regarding the breadth of claims allowed in biotechnology patents. The patent position of a biotechnology company is highly uncertain and involves complex legal and factual questions.

Currently, we hold 16 issued U.S. patents and 92 corresponding foreign patents. In accordance with ongoing research and development efforts, we have 39 pending U.S. patent applications and 192 corresponding foreign applications covering relevant and newly developed portions of its transgenic technology. Several of these pending applications are included in cross-licensing arrangements with other companies that in turn provide access to their proprietary technologies. Our more recently issued U.S. patents provide claim coverage for protein purification from the milk of transgenic animals, the production of monoclonal and assembled antibodies at commercial levels in the milk of transgenic mammals, the production of ATryn® in the milk of transgenic goats and one covering the production of Prolactin in the milk of transgenic animals. We cannot be certain that we will receive issued patents based on pending or future applications. Our issued patents may not contain claims sufficiently broad to protect us against competitors with similar technology. Additionally, our patents, our partners' patents and patents for which we have license rights may be challenged, narrowed, invalidated or circumvented. Furthermore, rights granted under patents may not provide us with any competitive advantage.

We may have to initiate arbitration or litigation to enforce our patent and license rights. If our competitors file patent applications that claim technology also claimed by us, we may have to participate in interference or opposition proceedings to determine the priority of invention. An adverse outcome could subject us to significant liabilities to third parties and require us to cease using the technology or to license the disputed rights from third parties. We may not be able to obtain any required licenses on commercially acceptable terms or at all.

The cost to us of any litigation or proceeding relating to patent rights, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because of their substantially greater resources. Uncertainties resulting from the initiation and continuation of any pending patent or related litigation could have a material adverse effect on our ability to compete in the marketplace. The U.S. Patent and Trademark Office has declared an interference proceeding between Advanced Cell Technologies, Inc. (ACT) and Geron Corporation for one of the patents we license from ACT. While we have also licensed nuclear transfer technology from Pharming, we do not know at this time what impact, if any, this interference proceeding may have on our ability to practice nuclear transfer for the production of animals expressing therapeutic proteins in their milk.

We rely on certain proprietary trade secrets and know-how that are not patentable. We have taken measures to protect our unpatented trade secrets and know-how, including having our employees, consultants and some contractors execute confidentiality agreements. These agreements could be breached. If so, it is possible that our remedies for a given breach might be inadequate. It is also

possible that competitors could independently develop or discover our trade secrets or that the trade secrets could otherwise become known.

Recovery from any catastrophic event may not be adequate.

While we have measures in place to minimize and recover from catastrophic events that may substantially destroy our animal herd(s), these measures may not be adequate to recover our production processes quickly enough to support critical timelines, collaborator needs or market demands. These catastrophic events may include diseases that breach our biosecurity measures or weather events such as tornadoes, earthquakes or fires. In addition, these catastrophic events may render some or all of the products at the affected facilities unusable.

Successful commercialization of our products will depend on obtaining coverage and reimbursement for use of the products from third-party payors.

Sales of pharmaceutical products depend largely on the reimbursement of patients' medical expenses by government health care programs and private health insurers. It is possible that third party payors will not reimburse sales of our transgenic products. Reimbursement by third party payors depends on a number of factors, including the payor's determination that use of the product is safe and effective, not experimental or investigational, medically necessary, appropriate for the specific patient and cost-effective. Reimbursement in the United States or foreign countries may not be available or maintained for any of our product candidates. If we do not obtain approvals for adequate third party reimbursements, we may not be able to establish or maintain price levels sufficient to realize an appropriate return on our or our partners' investment in product development. Any limits on reimbursement available from third party payors may reduce the demand for, or negatively affect the price of, our or our partners' products. Without the financial support of the government or third party insurers, the market for transgenic products will be limited.

The U.S. federal government and private insurers are continually working on ways to contain health care costs, particularly by limiting both coverage and the level of reimbursement for new therapeutic products. The government or private insurers may institute future price controls and other cost-containment measures on Medicare, Medicaid and other health care insurance spending. These controls and limits could affect the payments we collect from sales of our products. Internationally, medical reimbursement systems vary significantly, with some medical centers having fixed budgets, regardless of levels of patient treatment, and other countries requiring application for, and approval of, government or third party reimbursement. Even if we or our partners succeed in bringing transgenic products to market, uncertainties regarding future health care policy, legislation and regulation, as well as private market practices, could affect our ability to sell our products in commercially acceptable quantities at profitable prices.

The manufacture and sale of our products may expose us to product liability claims for which we could have substantial liability.

We face an inherent risk of product liability exposure related to testing of our transgenic product candidates in human clinical trials and will face even greater risks when we commercialize our products derived from these product candidates. An individual may bring a product liability claim against us if one of our products or product candidates causes, or is claimed to have caused, an injury or is found to be unsuitable for consumer use. Although we have obtained product liability insurance under an insurance policy arrangement with Genzyme Corporation and Genzyme's affiliates, it is possible that our insurance coverage will not be sufficient to cover any claim. Any product liability claim brought against us, with or without merit, could result in:

- liabilities that substantially exceed our product liability insurance, which we would then be required to pay from other sources, if available;
- an increase of our product liability insurance rates or the inability to maintain insurance coverage in the future on acceptable terms or at all;
- damage to our reputation and the reputation of our products, resulting in lower sales;
- regulatory investigations that could require costly recalls or product modifications; and
- the diversion of management's attention from managing our business.

Qualified managerial and scientific personnel are scarce in our industry.

We are highly dependent on the principal members of our scientific and management staff. Our success will depend in part on our ability to identify, attract and retain qualified managerial and scientific personnel. There is intense competition for qualified personnel in our industry. We may not be able to continue to attract and retain personnel with the advanced technical qualifications or managerial expertise necessary for the development of our business. If we fail to attract and retain key personnel, it could have a material adverse effect on our business, financial condition and results of operations. We have employment agreements with our executive officers, but these agreements do not guarantee that they will remain employed with us in the future. If we lose an executive officer, or a significant number of any of our staff, or are unable to hire and retain qualified personnel, then our ability to develop and commercialize our products and processes may be delayed or impaired. We do not carry key man insurance.

Genzyme's significant ownership interest in us could give it significant influence over matters requiring stockholder approval.

Genzyme is our largest single stockholder, beneficially owning 5,443,243 shares or 16.8% of our outstanding common stock at December 12, 2003, assuming the exercise of its 518,324 currently exercisable common stock purchase warrants with exercise prices ranging from \$6.30 to \$2.84. As a 16.8% shareholder, Genzyme's ownership interest could give it significant influence if it were to oppose matters requiring our stockholders' approval, including electing directors, adopting or amending provisions of our charter or by-laws and approving or preventing some mergers or similar transactions, such as a sale of substantially all of our assets, or transactions that could give our stockholders the opportunity to realize a premium over the market price of their shares.

We have obligations to issue shares of common stock in the future that will dilute your ownership interest and may adversely affect our stock price.

Sales of substantial amounts of our common stock in the public market, or the perception that such sales may occur, could adversely affect our common stock's market price. As of December 12,

2003, there were 31,927,798 shares of our common stock outstanding. As of December 12, 2003, options to purchase an aggregate of 3,303,969 shares of common stock at varying exercise prices were outstanding; of this total, options to purchase 1,748,226 shares were immediately exercisable and these shares could be immediately resold into the public market. As of December 12, 2003, Genzyme held 4,924,919 shares of our common stock which could be sold into the public markets under Rule 144 of the Securities Act, but which are currently subject to a lock-up provision until April 2004. The lock-up provision will be released at an earlier date if the average of the prices of our daily high and low stock prices, as reported on The NASDAQ National Market, exceeds \$12.00 per share for 20 consecutive trading days. Genzyme is also entitled to registration rights with respect to some of these shares. An additional 518,324 shares of our common stock, issuable to Genzyme upon exercise of outstanding warrants, are also entitled to registration rights, which could expedite the resale of such shares into the public market.

In August 2003, we completed a private placement transaction in which we sold the Selling Stockholders 3,626,465 shares of our common stock and warrants to purchase an aggregate 961,009 shares of our common stock at an exercise price of \$3.30 per share. We agreed to register for resale the shares of common stock and the shares issuable under the warrants that were issued in the private placement transaction.

Our capital raising efforts may dilute stockholder interests.

If we raise additional capital by issuing equity securities, the issuance will result in ownership dilution to our existing shareholders. The extent of such dilution will vary based upon the amount of capital raised.

Our common stock may have a volatile public trading price and low trading volume.

Historically, the market price of our common stock has been highly volatile and the market for our common stock has experienced significant price and volume fluctuations, some of which are unrelated to our company's operating performance. Since January 1, 2001, the trading price of our stock has fluctuated from a high of \$15.50 to a low of \$0.61. It is likely that the market price of our common stock will continue to fluctuate in the future. Factors which may have a significant adverse effect on our common stock's market price, include:

- announcements by us or our competitors of technological innovations or new commercial products;
- developments concerning our proprietary rights, including patent and litigation matters;
- publicity regarding actual or potential results relating to our or our partners' products or compounds under development;
- an unexpected termination of one of our partnerships;
- regulatory developments in the United States and other countries;
- general market conditions; and
- quarterly fluctuations in our revenues and other financial results.

The average daily trading volume of our common stock for the three-month period ending December 19, 2003 was 130,136 shares.

Anti-takeover provisions in our charter and by-laws and Massachusetts law may result in management entrenchment and adversely affect our stock price.

Anti-takeover provisions in our charter, our by-laws and Massachusetts statutes could delay or make more difficult a merger, tender offer or proxy contest involving us. These provisions may delay or prevent a change of control without action by the stockholders, and may resist important changes stockholders seek to make if they are dissatisfied with the conduct of our management. Therefore, these provisions could result in the entrenchment of our management and adversely affect the price of our common stock.

Our charter grants authority to the board of directors to issue series of preferred stock with certain rights and privileges, including voting rights, as it deems appropriate. This authority may enable our board of directors to deter or delay a change in control despite a shift in stock ownership, as a result of an increase in the number of shares needed to gain voting control. This may have the effect of discouraging tender offers and proxy contests, and give management the power to reject certain transactions which might be desired by stockholders. This provision could also be deemed to benefit incumbent management to the extent it deters offers by persons who would wish to make changes in management or exercise control over management.

In addition, our by-laws may have the effect of preventing changes in our management because stockholders are required to give us written notice of any proposal or director nomination within a specified period of time before the annual meeting of stockholders, certain qualifications for a person to be elected to the board of directors must be established, and stockholders are prohibited from calling a special meeting of stockholders, unless the stockholder owns 90% of our outstanding voting stock.

Our stockholder rights plan is another anti-takeover device. It involves a distribution to our stockholders of certain rights to acquire shares of our capital stock in the event of an acquisition of a predetermined number of shares by an investor. The stockholder rights plan is designed to deter coercive takeover tactics and to encourage a party interested in acquiring the corporation to negotiate with the board of directors.

Certain Massachusetts corporate statutes provide anti-takeover protections. Our charter gives effect to a provision of Massachusetts law that places directors of publicly-held Massachusetts corporations into three classes of nearly equal sizes with staggered terms, thereby permitting only one-third of the board of directors to be elected at once. In addition, with certain exceptions, Massachusetts law prohibits a publicly-held Massachusetts corporation from engaging in a business combination transaction with an “interested stockholder” for a period of three years. An “interested stockholder” is a person who owns 5% or more of the outstanding voting stock of the corporation. Finally, our by-laws include a provision excluding us from the applicability of a Massachusetts statute that denies voting rights to any person acquiring 20% or more of the outstanding voting stock of a corporation, unless such voting rights are approved by a majority of the corporation’s disinterested shareholders. Our by-laws may be amended at any time to subject us to this statute prospectively.

FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements that involve risks and uncertainties. These include statements about our expectations, plans, objectives, assumptions or future events. In some cases, you can identify forward-looking statements by terminology such as “anticipate,” “estimate,” “plans,” “potential,” “projects,” “continuing,” “ongoing,” “expects,” “management believes,” “we believe,” “we intend” and similar expressions. These statements involve estimates, assumptions and uncertainties that could cause actual results to differ materially from those expressed for the reasons described in this prospectus. You should not place undue reliance on these forward-looking statements.

You should be aware that our actual results could differ materially from those contained in the forward-looking statements due to a number of factors, including:

- failure to obtain government regulatory approvals;
- failure to achieve positive results in clinical trials;
- our ability to enter into future collaborative arrangements;
- competitive factors;
- our ability to raise additional capital;
- uncertainty regarding our patents and patent rights; and
- relationships with our consultants, academic collaborators and other third-party service providers.

You should also consider carefully the statements under “Risk Factors” and other sections of this prospectus, which address additional factors that could cause our actual results to differ from those set forth in the forward-looking statements and could materially and adversely affect our business, operating results and financial condition. All subsequent written and oral forward-looking statements attributable to us or persons acting on our behalf are expressly qualified in their entirety by the applicable cautionary statements.

The forward-looking statements speak only as of the date on which they are made, and, except to the extent required by federal securities laws, we undertake no obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

USE OF PROCEEDS

Unless we indicate otherwise in the applicable prospectus supplement, we expect to use the net proceeds of this offering as follows:

- to fund research and product development activities;
- to fund preclinical studies and clinical trials of our product candidates;
- to fund investment in capital equipment;
- expand our facilities, as needed, and hire additional personnel;
- to provide working capital; and
- for general corporate purposes which may include acquisitions of other businesses and complementary technologies or products.

We have not determined the amount of net proceeds to be used for each of the specific purposes listed. Accordingly, we will have broad discretion to use the proceeds as we see fit.

The amounts and timing of our actual expenditures will depend upon a number of factors, including:

- the scope and results of preclinical studies and clinical trials,
- the progress of research and development activities,
- the cost, timing and outcomes of regulatory review,
- the rate of technological advances,
- determinations as to the commercial potential of our products under development,
- administrative and legal expenses,
- the status of competitive products,
- the establishment of manufacturing capacity or third-party manufacturing arrangements,
- the establishment of collaborative arrangements with other companies, and
- the availability of other financing.

We will require substantial additional funds to conduct our operations in the future. We intend to invest the net proceeds in interest-bearing, investment-grade interest-bearing instruments.

PLAN OF DISTRIBUTION

We may sell the securities being offered by us in this prospectus:

- directly to purchasers;
- through agents;
- through dealers;
- through underwriters; or
- through a combination of any of these methods of sale.

We and our agents and underwriters may sell the securities being offered by us in this prospectus from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to the prevailing market prices; or
- at negotiated prices.

We may solicit directly offers to purchase securities. We may also designate agents from time to time to solicit offers to purchase securities. Any agent, who may be deemed to be an “underwriter” as that term is defined in the Securities Act, may then resell the securities to the public at varying prices to be determined by that agent at the time of resale.

If we use underwriters to sell securities, we will enter into an underwriting agreement with them at the time of the sale to them. The names of the underwriters will be set forth in the prospectus supplement that will be used by them together with this prospectus to make resales of the securities to the public. In connection with the sale of the securities offered, these underwriters may be deemed to

have received compensation from us in the form of underwriting discounts or commissions. Underwriters may also receive commissions from purchasers of the securities.

Underwriters may also use dealers to sell securities. If this happens, these dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they may act as agents.

Any underwriting compensation paid by us to underwriters in connection with the offering of the securities offered in this prospectus, and any discounts, concessions or commissions allowed by underwriters to participating dealers, will be set forth in the applicable prospectus supplement.

Underwriters, dealers, agents and other persons may be entitled, under agreements that may be entered into with us, to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments that they may be required to make in respect of these liabilities. Underwriters and agents may engage in transactions with, or perform services for, us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters, dealers, or other persons to solicit offers by certain institutions to purchase the securities offered by us under this prospectus pursuant to contracts providing for payment and delivery on a future date or dates. The obligations of any purchaser under any these contracts will be subject only to those conditions described in the applicable prospectus supplement, and the prospectus supplement will set forth the price to be paid for securities pursuant to these contracts and the commissions payable for solicitation of these contracts.

Any underwriter may engage in over-allotment, stabilizing and syndicate short covering transactions and penalty bids in accordance with Regulation M of the Securities Exchange Act of 1934, as amended. Over-allotment involves sales in excess of the offering size, which creates a short position. Stabilizing transactions involve bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Syndicate short covering transactions involve purchases of securities in the open market after the distribution has been completed in order to cover syndicate short positions. Penalty bids permit the underwriters to reclaim selling concessions from dealers when the securities originally sold by the dealers are purchased in covering transactions to cover syndicate short positions. These transactions may cause the price of the securities sold in an offering to be higher than it would otherwise be. These transactions, if commenced, may be discontinued by the underwriters at any time.

Any shares of securities sold pursuant to a prospectus supplement will be listed on The NASDAQ National Market, subject to official notice of issuance.

The anticipated date of delivery of the securities offered hereby will be set forth in the applicable prospectus supplement relating to each offering.

LEGAL MATTERS

The validity of the common stock offered hereby will be passed upon by Palmer & Dodge LLP, Boston, Massachusetts, our counsel. Nathaniel S. Gardiner, a partner of Palmer & Dodge LLP, is our Clerk.

EXPERTS

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 29, 2002 have been so incorporated in reliance on the reports of PricewaterhouseCoopers LLP, independent accountants, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the Securities and Exchange Commission. Our website is www.gtc-bio.com and through the Investor Information portion of our website, you may access, free of charge, our filings, as soon as reasonably practicable after we electronically file such materials with, or furnish them to, the SEC. You may also read and copy any document we file at the SEC's Public Reference Room at 450 Fifth Street, N.W., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information. Our SEC filings are also available to the public at the SEC's web site at <http://www.sec.gov>. Our common stock is listed on The NASDAQ National Market. Reports and other information concerning us can be inspected at the offices of The NASDAQ National Market.

INCORPORATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. We incorporate by reference the documents listed below and any future filings made with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act, provided, however, that we are not incorporating any information furnished under Item 9 or Item 12 of any Current Report on Form 8-K.

- (a) Our Annual Report on Form 10-K for the fiscal year ended December 29, 2002, filed with the Commission on March 28, 2003;
- (b) Our Quarterly Report on Form 10-Q for the quarterly period ended March 30, 2003, filed with the Commission on May 6, 2003;
- (c) Our Proxy Statement on Schedule 14A filed with the Commission on April 23, 2003;
- (d) Our Current Report on Form 8-K filed with the Commission on August 4, 2003;
- (e) Our Quarterly Report on Form 10-Q for the quarterly period ended June 29, 2003, filed with the Commission on August 5, 2003;
- (f) Our Quarterly Report on Form 10-Q/A for the quarterly period ended June 29, 2003, filed with the Commission on November 26, 2003.
- (g) Our Quarterly Report on Form 10-Q for the quarterly period ended September 28, 2003, filed with the Commission on November 12, 2003;
- (h) The description of our common stock in our registration statement on Form 8-A, filed on May 19, 1993, including any amendment or reports filed for the purpose of updating this description; and
- (i) The description of our Series C junior participating cumulative preferred stock purchase rights in our registration statement on Form 8-A, filed on June 1, 2001.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address:

John B. Green
Senior Vice President, Chief Financial Officer and Treasurer
GTC Biotherapeutics, Inc.
175 Crossing Boulevard
Framingham, Massachusetts 01702
(508) 620-9700

PART II

Item 14. Other Expenses of Issuance and Distribution

The expenses in connection with the securities being registered are as set forth in the following table. All of the amounts shown are estimates except the SEC registration fee.

SEC registration fee	\$ 3,236
Accounting fees and expenses	50,000
Legal fees and expenses	50,000
Printing expenses	50,000
Miscellaneous expenses	15,000
Total	<u>\$ 168,236</u>

Item 15. Indemnification of Directors and Officers

Section 67 of chapter 156B of the Massachusetts Business Corporation Law grants the Company the power to indemnify any director, officer, employee or agent to whatever extent permitted by the Company's Restated Articles of Organization, Bylaws or a vote adopted by the holders of a majority of the shares entitled to vote thereon, unless such indemnitee has been adjudicated in any proceeding not to have acted in good faith in the reasonable belief that his or her actions were in the best interests of the corporation or, to the extent that the matter for which indemnification is sought relates to service with respect to an employee benefit plan, in the best interests of the participants or beneficiaries of such employee benefit plan. Such indemnification may include payment by the Company of expenses incurred in defending a civil or criminal action or proceeding in advance of the final disposition of such action or proceeding, upon receipt of an undertaking by the person indemnified to repay such payment if he or she shall be adjudicated to be not entitled to indemnification under the statute.

Article VI of the Company's Bylaws provides that the Company shall, to the extent legally permissible, indemnify each person who may serve or who has served at any time as a director or officer of the Company or of any of our subsidiaries, or who at the request of the Company may serve or at any time has served as a director, officer or trustee of, or in a similar capacity with, another organization or an employee benefit plan, against all expenses and liabilities (including counsel fees, judgments, fines, excise taxes, penalties and amounts payable in settlements) reasonably incurred by or imposed upon such person in connection with any threatened, pending or completed action, suit or other proceeding, whether civil, criminal, administrative or investigative, in which he or she may become involved by reason of his or her serving or having served in such capacity (other than a proceeding voluntarily initiated by such person unless he or she is successful on the merits, the proceeding was authorized by the Company or the proceeding seeks a declaratory judgment regarding his or her own conduct). No indemnification, however, shall be provided for any such person with respect to any matter as to which he or she shall have been finally adjudicated in any proceeding not to have acted in good faith in the reasonable belief that his or her action was in the best interests of the Company or, to the extent such matter relates to service with respect to any employee benefit plan, in the best interests of the participants or beneficiaries of such employee benefit plan. Such indemnification shall include payment by the Company of expenses incurred in defending a civil or criminal action or proceeding in advance of the final disposition of such action or proceeding, upon receipt of an undertaking by the person indemnified to repay such payment if he or she shall be adjudicated to be not entitled to indemnification under this article, which undertaking may be accepted without regard to the financial ability of such person to make repayment.

The indemnification under Article VI of the Bylaws is a contract right inuring to the benefit of the directors, officers and other persons entitled to be indemnification. In addition, the indemnification is

expressly not exclusive of any other rights to which such director, officer or other person may be entitled.

The Company also has in place agreements with certain directors which affirm the Company's obligation to indemnify them to the fullest extent permitted by law and contain various procedural and other provisions which expand the protection afforded by the Company's Bylaws.

Section 13(b)(1½) of chapter 156B of the Massachusetts Business Corporation Law provides that a corporation may, in its Articles of Organization, eliminate or limit a director's personal liability to the corporation and its stockholders for monetary damages for breaches of fiduciary duty, except in circumstances involving (i) a breach of the director's duty of loyalty to the corporation or its stockholders, (ii) acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) unauthorized distributions and loans to insiders and (iv) transactions from which the director derived an improper personal benefit. Section 6.5 of GTC's Restated Articles of Organization provides that a director shall not be liable to the Company or its stockholders for monetary damages for any breach of fiduciary duty as a director, except to the extent that such elimination or limitation of liability is not permitted under the Massachusetts Business Corporation Law as in effect when such liability is determined.

Item 16. Exhibits

<u>Exhibit Number</u>	<u>Description</u>
4.1.1	Restated Articles of Organization of GTC, filed with the Secretary of the Commonwealth of Massachusetts on December 27, 1993. Filed as Exhibit 3.1 to the Company's Annual Report on Form 10-K for the year ended December 31, 1993 (File No. 0-21794) and incorporated herein by reference.
4.1.2	Articles of Amendment to the Restated Articles of Organization of GTC filed with the Secretary of the Commonwealth of Massachusetts on October 3, 1994. Filed as Exhibit 3.1.2 to GTC's Annual Report on Form 10-K for the year ended December 28, 1997 (File No. 0-21794) and incorporated herein by reference.
4.1.3	Articles of Amendment to the Restated Articles of Organization filed with the Secretary of Commonwealth of Massachusetts on June 26, 1997. Filed as Exhibit 3 to GTC's Quarterly Report on Form 10-Q for the quarter ended June 29, 1997 (File No. 0-21794) and incorporated herein by reference.
4.1.4	Articles of Amendment to the Restated Articles of Organization of GTC filed with the Secretary of the Commonwealth of Massachusetts on June 1, 2000. Filed as Exhibit 4.1.5 to GTC's Registration Statement on Form S-8 filed with the Commission on June 2, 2000 (File No. 333-38490) and incorporated herein by reference.
4.1.5	Certificate of Vote of Directors Establishing a Series of a Class of Stock of GTC and designating the Series C Junior Participating Cumulative Preferred Stock. Filed as Exhibit 3.1 to GTC's Current Report on Form 8-K filed on June 1, 2001 (File No. 0-21794) and incorporated herein by reference.
4.1.6	Articles of Amendment to the Restated Articles of Organization of GTC filed with the Secretary of the Commonwealth of Massachusetts on May 31, 2002. Filed as Exhibit 3.1 to the GTC's Current Report on Form 8-K filed on June 3, 2002 (File No. 0-21794) and incorporated herein by reference.
4.2	By-Laws of GTC, as amended. Filed as Exhibit 3.1 to GTC's Form 10-Q for the quarter ended July 4, 1999 (File No. 0-21794) and incorporated herein by reference.
4.3	Specimen Common Stock Certificate. Filed as Exhibit 4.1 to GTC's Registration Statement on Form S-1 (File No. 33-62782) and incorporated herein by reference.
4.4	Shareholder Rights Agreement, dated as of May 31, 2001, between GTC and American Stock Transfer and Trust Company, as Rights Agent. Filed as Exhibit 4.1 to GTC's Current Report on Form 8-K filed on June 1, 2001 (File No. 0-21794) and incorporated herein by reference.
5	Opinion of Palmer & Dodge LLP as to the legality of the securities registered hereunder. Filed herewith.
23.1	Consent of PricewaterhouseCoopers LLP, independent accountants. Filed herewith.
23.2	Consent of Palmer & Dodge LLP (contained in Opinion of Palmer & Dodge LLP filed as Exhibit 5.1).
24	Power of Attorney (set forth on the Signature Page to this Registration Statement).

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes as follows:

(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 hereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in this Registration Statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement;

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

Provided, however, That paragraphs (a)1(i) and (a)1(ii) of this section do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in periodic reports filed with or furnished to the Commission by the registrant pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended 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.

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

(b) The undersigned 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 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.

(c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers or controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Commission such indemnification is against public policy as expressed in the Act 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 our counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Act and will be governed by the final adjudication of such issue.

(d) 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 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 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, as amended, 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 Town of Framingham, Commonwealth of Massachusetts, on December 23, 2003.

GTC BIOTHERAPEUTICS, INC.

By: /s/ GEOFFREY F. COX

Geoffrey F. Cox
*Chairman of the Board, President
and Chief Executive Officer*

POWER OF ATTORNEY

We, the undersigned officers and directors of GTC Biotherapeutics, Inc., hereby severally constitute and appoint Geoffrey F. Cox, John B. Green and Nathaniel S. Gardiner, and each of them singly, our true and lawful attorneys-in-fact, with full power to them in any and all capacities, to sign any amendments to this Registration Statement on Form S-3 (including any post-effective amendments thereto), and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact may do or cause to be done by virtue hereof.

Witness our hands and common seal on the dates set forth below.

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

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ GEOFFREY F. COX</u> Geoffrey F. Cox	Chairman of the Board, President and Chief Executive Officer (principal executive officer)	December 23, 2003
<u>/s/ JOHN B. GREEN</u> John B. Green	Senior Vice President, Chief Financial Officer and Treasurer (principal financial and accounting officer)	December 23, 2003
<u>/s/ JAMES A. GERAGHTY</u> James A. Geraghty	Director	December 23, 2003
<u>/s/ ROBERT W. BALDRIDGE</u> Robert W. Baldrige	Director	December 23, 2003
<u>/s/ ALAN W. TUCK</u> Alan W. Tuck	Director	December 23, 2003
<u>/s/ FRANCIS J. BULLOCK</u> Francis J. Bullock	Director	December 23, 2003
<u>/s/ PAMELA W. MCNAMARA</u> Pamela W. McNamara	Director	December 23, 2003
<u>/s/ MARVIN L. MILLER</u> Marvin L. Miller	Director	December 23, 2003

Exhibit Index

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PALMER & DODGE LLP

111 HUNTINGTON AVENUE AT PRUDENTIAL CENTER
BOSTON, MA 02199-7613

December 23, 2003

GTC Biotherapeutics, Inc.
175 Crossing Boulevard
Framingham, MA 01702

Ladies and Gentlemen:

We are furnishing this opinion in connection with the registration statement on Form S-3 (the "Registration Statement") of GTC Biotherapeutics, Inc., a Massachusetts corporation (the "Company"), filed on or about the date hereof with the U.S. Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended (the "Securities Act").

We have reviewed the Registration Statement, including the prospectus (the "Prospectus") that is a part of the Registration Statement. The Prospectus provides that it will be supplemented in the future by one or more supplements to the Prospectus (each a "Prospectus Supplement"). The Prospectus as supplemented by various Prospectus Supplements will provide for the issuance and sale of up to \$40,000,000 aggregate offering price of shares of the Company's common stock, \$.01 par value (the "Common Stock").

In our capacity as your counsel in connection with such registration, we are familiar with certain proceedings taken and proposed to be taken by the Company in connection with the authorization of the Common Stock. We have made such examination as we consider necessary to render this opinion.

The opinions rendered herein are limited to Massachusetts law and the federal laws of the United States.

Based upon the foregoing, we are of the opinion that the Company has the authority pursuant to its Articles of Organization, as amended, to issue up to a total of 100,000,000 shares of Common Stock. Upon adoption by the Board of Directors of the Company of a resolution in form and content as required by applicable law and upon issuance and delivery of and payment for such shares in the manner contemplated by the Registration Statement, the Prospectus and the related Prospectus Supplement(s) and by such resolution, such shares of Common Stock will be validly issued, fully paid and nonassessable.

The foregoing opinions are subject to: (i) the effect of bankruptcy, insolvency, reorganization, fraudulent conveyance, moratorium or other similar laws now or hereafter in effect relating to or affecting the rights and remedies of creditors; (ii) general principles of equity (whether considered in a proceeding in equity or at law); and (iii) the unenforceability under certain circumstances under law or court decisions of provisions providing for the indemnification of, or contribution to, a party with respect to a liability where such indemnification or contribution is contrary to public policy. We express no opinion concerning the enforceability of any waiver of rights or defenses with respect to stay, extension or usury laws.

We assume for purposes of this opinion that the Company is and will remain duly organized, validly existing and in good standing under Massachusetts law.

We hereby consent to your filing this opinion as an exhibit to the Registration Statement and to the reference to our firm under the caption “Legal Matters” in the Prospectus included therein.

Very truly yours,

/s/ PALMER & DODGE LLP

PALMER & DODGE LLP

CONSENT OF INDEPENDENT ACCOUNTANTS

We hereby consent to the incorporation by reference in this Registration Statement on Form S-3 of our reports dated March 4, 2003 relating to the financial statements and financial statement schedule, which appear in GTC Biotherapeutics Inc.'s Annual Report on Form 10-K for the year ended December 29, 2002. We also consent to the reference to us under the heading "Experts" in such Registration Statement.

/s/ PricewaterhouseCoopers LLP

PricewaterhouseCoopers LLP
Boston, Massachusetts
December 19, 2003