GENTA INC DE/
Form S-3/A
January 07, 2010

As filed with the Securities and Exchange Commission on January 7, 2010
Registration Statement No. 333-163995

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

AMENDMENT NO. 1

TO

FORM S-3

REGISTRATION STATEMENT
UNDER THE SECURITIES ACT OF 1933

Genta Incorporated
(Exact name of Registrant as Specified in Its Charter)

Delaware	2836	33-0326866
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code)	(I.R.S. Employer Identification No.)

200 Connell Drive
Berkeley Heights, NJ 07922
(908) 286-9800
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Raymond P. Warrell, Jr., M.D.
Chairman and Chief Executive Officer
Genta Incorporated
200 Connell Drive
Berkeley Heights, NJ 07922
(908) 286-9800
(Name, address, including zip code, and telephone number including area code, of agent for service)

Copies to:
Emilio Ragosa, Esq.
Morgan, Lewis & Bockius LLP

502 Carnegie Center
Princeton, New Jersey 08540
(609) 919-6600

Approximate date of commencement of proposed sale to public : From time to time or at one time after this registration statement becomes effective in light of market conditions and other factors.

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

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 (the “Securities Act”), other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. x

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

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

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. ¨

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of “smaller reporting company, accelerated filer and large accelerated filer” in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer (Do not check if smaller reporting company)	Smaller reporting company x

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Proposed maximum aggregate offering price (1)(2)(3)	Amount of registration fee
Common Stock, par value $0.001 per share (4)	(5)	
Preferred Stock, par value $0.001 per share (6)	(5)	
Debt Securities (7)	(5)	
Warrants (8)	(5)	
Units (9)		
Totals	$ 50,000,000	$ 3,565.00 (10)

(1) The proposed maximum offering price will be determined from time to time by the Registrant in connection with the issuance of securities registered under this registration statement.
(2) Estimated solely for purposes of calculating the amount of the registration fee pursuant to Rule 457(o) promulgated under the Securities Act of 1933, as amended.
(3) In no event will the aggregate initial offering price of all securities issued from time to time pursuant to this registration statement exceed $50,000,000.00. Securities registered under this registration statement may be sold separately, or together. This total amount also includes such securities as may, from time to time, be issued upon conversion or exchange of securities registered under this registration statement, to the extent any such securities are, by their terms, convertible into or exchangeable for other securities.
(4) An indeterminate number of shares of common stock of the Registrant as may be sold from time to time are being registered under this registration statement. Also includes such indeterminate number of shares of common stock as may be (a) issued upon conversion, redemption or exchange for any debt securities, preferred stock or other securities that provide for conversion or exchange into common stock, (b) issued upon exercise and settlement of any warrants or (c) issued as a result of stock splits, stock dividends or similar transactions.
(5) Not required to be included pursuant to General Instruction II.D. of Form S-3 under the Securities Act of 1933, as amended.
(6) An indeterminate number of shares of preferred stock of the Registrant as may be sold from time to time are being registered under this registration statement. Also includes such indeterminate number of shares of preferred stock as may be (a) issued upon conversion, redemption or exchange for any debt securities, preferred stock or other securities that provide for conversion or exchange into preferred stock, (b) issued upon exercise and settlement of any warrants or (c) issued as a result of stock splits, stock dividends or similar transactions.
(7) An indeterminate principal amount of debt securities of the Registrant as may be sold from time to time are being registered under this registration statement. If any debt securities of the Registrant are issued at an original issue discount, then the offering price shall be in such greater principal amount as shall result in an aggregate initial offering price not to exceed $50,000,000.00, less the dollar amount of any securities previously issued under this registration statement.
(8) An indeterminate number of warrants of the Registrant as may be sold from time to time are being registered under this registration statement. Warrants may be exercised to purchase common stock, preferred stock or debt securities.
(9) Each unit will be issued under a unit agreement or indenture and will represent an interest in one or more debt securities, warrants, preferred shares and common shares, as well as debt or equity securities of an entity affiliated or not affiliated with the Registrant, in any combination, which may or may not be separable from one another.
(10) A registration fee of $3,565.00 was previously paid by the Registrant with the initial filing of this registration statement on Form S-3 (File No. 333-163995), which was filed by the Registrant on December 23, 2009.

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 is not soliciting an offer to buy the securities in any state where the offer or sale is not permitted.

Subject to Completion, dated January 7, 2010

PROSPECTUS

GENTA INCORPORATED

$50,000,000
DEBT SECURITIES
WARRANTS
PREFERRED STOCK
COMMON STOCK
UNITS

Genta Incorporated may from time to time offer to sell debt securities, warrants, preferred stock, common stock and/or units, separately or together in one or more combinations. The debt securities, warrants and preferred stock may be convertible into or exercisable or exchangeable for common stock or preferred stock or other securities of Genta Incorporated or any other party identified in the applicable prospectus supplement.

Our common stock is traded on the OTC Bulletin Board under the symbol “GETA.OB”. The closing price of our common stock on December 16, 2009 was $0.08 per share. Our principal offices are located at 200 Connell Drive, Berkeley Heights, New Jersey 07922. Our telephone number is (908) 286-9800.

The total amount of debt securities, warrants, preferred stock, common stock and units will have an initial aggregate offering price of up to $50,000,000.00, or the equivalent amount in other currencies, currency units or composite currencies.

The securities covered by this prospectus may be offered and sold to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continuous or delayed basis.

This prospectus describes some of the general terms that may apply to these securities and the general manner in which they may be offered. The specific terms of any securities to be offered, and the specific manner in which they may be offered, will be described in one or more supplements to this prospectus.

INVESTING IN OUR SECURITIES INVOLVES A HIGH DEGREE OF RISK. RISKS ASSOCIATED WITH AN INVESTMENT IN OUR SECURITIES WILL BE DESCRIBED IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND CERTAIN OF OUR FILINGS WITH THE SECURITIES AND EXCHANGE COMMISSION, AS DESCRIBED UNDER THE SECTION ENTITLED “RISK FACTORS” ON PAGE 14 OF THIS PROSPECTUS. THE PROSPECTUS SUPPLEMENT APPLICABLE TO EACH TYPE OR SERIES OF SECURITIES WE OFFER MAY CONTAIN A DISCUSSION OF ADDITIONAL RISKS APPLICABLE TO AN INVESTMENT IN US AND THE PARTICULAR TYPE OF SECURITIES WE ARE OFFERING UNDER THAT PROSPECTUS SUPPLEMENT.

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.

The date of this prospectus is January 7, 2010

EXPLANATORY NOTE

The prospectus contained herein relates to the general description of debt securities, warrants, preferred stock, common stock and units issuable by Genta Incorporated.

To the extent required, the information in the prospectus, including financial information, will be updated at the time of each offering. Upon each such offering, a prospectus supplement to the base prospectus will be filed.

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You should rely only on the information provided in this prospectus and the prospectus supplement, as well as the information incorporated by reference. We have not authorized anyone to provide you with different information. We are not making an offer of these securities in any jurisdiction where the offer is not permitted. You should not assume that the information in this prospectus, the prospectus supplement or any documents incorporated by reference is accurate as of any date other than the date of the applicable document.

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3/A that we filed with the U.S. Securities and Exchange Commission, referred to herein as the SEC, using a "shelf" registration process. Under a shelf registration process, we may issue, in one or more offerings, any combination of senior or subordinated debt securities, warrants, preferred stock, common stock or units, collectively referred to herein as the securities, up to a total dollar amount of $50,000,000.00.

Each time we sell these securities we will provide you with a prospectus supplement containing specific information about the terms of each such sale. This prospectus may not be used to sell any of the securities unless accompanied by a prospectus supplement. The prospectus supplement also may add, update or change information in this prospectus. If there is any inconsistency between the information in the prospectus and the prospectus supplement, you should rely on the information in the prospectus supplement. You should read both this prospectus and any prospectus supplement together with additional information described under the heading "Where You Can Find More Information; Incorporation of Documents by Reference" beginning on page 48 of this prospectus.

Unless otherwise indicated or unless the context otherwise requires, all references in this prospectus to "Genta," "we," "us," or similar references mean Genta Incorporated and our subsidiaries.

You should rely only on the information contained in this prospectus or in a prospectus supplement or amendment. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. We may offer to sell, and seek offers to buy these securities only in jurisdictions where offers and sales are permitted. The information contained in this prospectus or a prospectus supplement or amendment or incorporated herein by reference is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of securities.

ABOUT GENTA INCORPORATED

GENERAL

Overview

We are a biopharmaceutical company engaged in pharmaceutical (drug) research and development. We are dedicated to the identification, development and commercialization of novel drugs for the treatment of cancer and related diseases. Our research portfolio consists of two major programs: "DNA/RNA Medicines" (which includes our lead oncology drug, Genasense ®); and "Small Molecules" (which includes our marketed product, Ganite ® , and tesetaxel and oral gallium-containing compounds).

The DNA/RNA Medicines program includes drugs that are based on using modifications of either DNA or RNA as drugs that can be used to treat disease. These technologies include antisense, decoys, and small interfering or micro RNAs. Our lead drug from this program is an investigational antisense compound known as Genasense ® (oblimersen sodium injection). Genasense ® is designed to disrupt a specific mRNA, which then block the production of a protein known as Bcl-2. Current science suggests that Bcl-2 is a fundamental (although not sole) cause of the inherent resistance of cancer cells to anticancer treatments, such as chemotherapy, radiation, and monoclonal antibodies. While Genasense ® has displayed anticancer activity when used alone, we are developing the drug primarily as a means of amplifying the cytotoxic effects of other anticancer treatments. We are also developing tesetaxel as an oral agent that targets tubulin in cancer cells, an extremely well-validated cancer target. Oral gallium compounds employ the same active ingredient in our marketed product, Ganite ® , that has demonstrated clinical activity in a range of diseases associated with accelerated bone loss.

Genasense ®

For the past several years, we have sought to secure regulatory approval for the marketing of Genasense ® . Genasense ® has been studied in combination with a wide variety of anticancer drugs in a number of different cancer indications. We have reported results from randomized trials of Genasense ® in a number of diseases. Under our own sponsorship or in collaboration with others, we are currently conducting additional clinical trials. We are especially interested in the development, regulatory approval, and commercialization of Genasense ® in at least three diseases: melanoma; chronic lymphocytic leukemia (CLL); and non-Hodgkin’s lymphoma (NHL).

Melanoma

Our major current initiative is a randomized controlled trial that tests whether the addition of Genasense ® to standard chemotherapy can improve outcomes for patients with advanced melanoma. In August 2007, we initiated a new Phase 3 trial of Genasense ® plus chemotherapy in advanced melanoma. This trial, known as AGENDA, is a randomized, double-blind, placebo-controlled study in which patients are randomly assigned to receive Genasense ® plus dacarbazine or dacarbazine alone. The study uses LDH, a blood enzyme associated with progressive melanoma, as a biomarker to identify patients who are most likely to respond to Genasense ® , based on data obtained from our preceding trial in melanoma.

The design of AGENDA was based on data obtained from a similarly designed Phase 3 trial that was published in 2006. Results from this antecedent study showed that treatment with Genasense ® plus dacarbazine compared with dacarbazine alone was associated with a statistically significant increase in overall response, complete response, durable response, and progression-free survival (PFS). However, the primary endpoint of overall survival approached but did not quite reach statistical significance (P=0.077) in the entire “intent-to-treat” population. Our analysis showed a significant treatment interaction effect related to LDH. This benefit was particularly noteworthy for patients whose baseline LDH did not exceed 80% of the upper limit of normal for this lab value.

In March 2009, we completed accrual of 314 patients into AGENDA. In October 2009, we announced that AGENDA did not show a statistically significant benefit for its co-primary endpoint of progression-free survival. Secondary endpoints of overall response rate and disease control rate (which includes complete and partial responses, plus stable disease greater than 3 months duration) also did not show a statistically significant benefit. According to the pre-specified analysis plan, the statistical significance of durable response (a secondary endpoint that measures the proportion of patients who achieved a complete or partial response that lasts greater than 6 months) was too early to evaluate. However, the observed differences in progression-free survival, overall response, disease control and durable response all numerically favored the group that received Genasense ® ..

Overall survival, the other co-primary endpoint in AGENDA, was also too early to evaluate, as prospectively specified. An analysis for futility, which was defined as greater than 50% conditional power to observe a statistically significant benefit of Genasense ® (P<0.05) under the prospectively specified hazard ratio of 0.69, was conducted for the co-primary endpoint of overall survival. AGENDA passed this futility analysis, and an Independent Data Monitoring Committee recommended that the trial continue to completion for the determination of the overall survival endpoint. The safety profile of Genasense ® in AGENDA was consistent with prior studies. Pending adequacy of financial resources and other contingencies noted herein, Genta currently intends to continue the AGENDA trial in order to determine whether the addition of Genasense® to dacarbazine is associated with a statistically significant increase in overall survival. If that association is demonstrated, we currently expect that Genta would submit regulatory applications for the marketing approval of Genasense® on a worldwide basis.

We have been conducting other trials of Genasense ® in melanoma including a Phase 2 trial of Genasense ® plus chemotherapy consisting of Abraxane ® (paclitaxel protein-bound particles for injectable suspension) (albumin bound) plus temozolomide (Temodar ®). We have expected to examine whether different dosing regimens would improve the dosing convenience. We are currently assessing whether to continue such trials.

CLL

As noted above, our NDA for the use of Genasense ® plus chemotherapy in patients with relapsed or refractory CLL was not approved. We conducted a randomized Phase 3 trial in 241 patients with relapsed or refractory CLL who were treated with fludarabine and cyclophosphamide (Flu/Cy) with or without Genasense ® . The trial achieved its primary endpoint: a statistically significant increase (17% vs. 7%; P=0.025) in the proportion of patients who achieved a

complete response (CR), defined as a complete or nodular partial response. Patients who achieved this level of response also experienced disappearance of predefined disease symptoms. A key secondary endpoint, duration of CR, was also significantly longer for patients treated with Genasense ® (median exceeding 36+ months in the Genasense ® group, versus 22 months in the chemotherapy-only group).

Several secondary endpoints were not improved by the addition of Genasense ® . The percentage of patients who experienced serious adverse events was increased in the Genasense ® arm; however, the percentages of patients who discontinued treatment due to adverse events were equal in the treatment arms. The incidence of certain serious adverse reactions, including but not limited to nausea, fever and catheter-related complications, was increased in patients treated with Genasense ® ..

We received a “non-approvable” notice from the FDA in December 2006 for our NDA that proposed the use of Genasense ® in combination with Flu/Cy for the treatment of patients with relapsed or refractory CLL who had previously received fludarabine. In June 2008, we announced results from 5 years of follow-up on patients who had been accrued to our completed Phase 3 trial. These data showed that patients treated with Genasense ® plus chemotherapy who achieved either a complete response (CR) or a partial response (PR) also achieved a statistically significant increase in survival with chemotherapy alone (median = 56 months vs. 38 months, respectively). After 5 years of follow-up, 22 of 49 (45%) responders in the Genasense ® group were alive compared with 13 of 54 (24%) responders in the chemotherapy-only group (hazard ratio = 0.6; P = 0.038). Moreover, with 5 years of follow-up, 12 of 20 patients (60%) in the Genasense ® group who achieved CR were alive, 5 of these patients remained in continuous CR without relapse, and 2 additional patients had relapsed but had not required additional therapy. By contrast, only 3 of 8 CR patients in the chemotherapy-only group were alive, all 3 had relapsed, and all 3 had required additional anti-leukemic treatment.

In March 2009, the FDA’s Center for Drug Evaluation and Research (CDER) decided that available data were still insufficient to support approval of Genasense ® in CLL, and the Agency recommended conducting another clinical trial. We have made no decision whether to conduct this study or whether to pursue this application without further study for regulatory approval in other territories.

As with melanoma, we believe the clinical activity in CLL, as well as in non-Hodgkin’s lymphoma and other types of cancer, should be explored with additional clinical research. We are currently reassessing whether to proceed with such studies.

NHL

Several trials have shown clinical activity of Genasense ® in patients with non-Hodgkin’s lymphoma (NHL). We would like to conduct additional clinical studies in patients with NHL to test whether Genasense ® can be approved in this indication.

Tesetaxel

In March 2008, we obtained an exclusive worldwide license for tesetaxel, a novel taxane compound that is taken by mouth. Tesetaxel has completed Phase 2 trials in a number of cancer types, and the drug has shown definite evidence of antitumor activity in gastric cancer and breast cancer. Tesetaxel also appears to be associated with a lower incidence of peripheral nerve damage, a common side effect of taxanes that limits the maximum amount of these drugs that can be given to patients. In January 2009, we announced initiation of a new clinical trial with tesetaxel to examine the clinical pharmacology of the drug over a narrow dosing range around the established Phase 2 dose. We expect accrual to the initial phase of this study to be complete in December 2009.

We have received approval by FDA for designation of tesetaxel as an Orphan Drug for treatment of patients with advanced melanoma. Our current priorities for clinical testing of tesetaxel includes the evaluation of safety and efficacy in patients with advanced gastric cancer, advanced melanoma, and prostate cancer. Other disease priorities for clinical research include cancers of the bladder and breast, among other disorders. Maintenance of the license from Daiichi Sankyo requires certain milestone payments. If such payments are not made, Daiichi Sankyo may elect to

terminate the license.

Oral Gallium-Containing Compounds

Our other pipeline products include novel oral formulations of gallium-containing compounds. We completed a single-dose Phase 1 study of an initial formulation of a new drug known as “G4544(a)”. We have formulated a modified version of this compound, known as “G4544(b)”, in order to test whether this compound will improve certain pharmaceutical characteristics.

If we are able to identify a clinically and commercially acceptable formulation of an oral gallium-containing compound, we may pursue a 505(b)(2) strategy to establish bioequivalence to our marketed product, Ganite ® , for its initial regulatory approval. We believe a drug of this type may also be broadly useful for treatment of other diseases associated with accelerated bone loss, such as bone metastases, Paget’s disease and osteoporosis. In addition, new uses of gallium-containing compounds have been identified for treatment of certain infectious diseases.

Ganite ®

We are currently marketing Ganite ® in the U.S., which is an intravenous formulation of gallium, for treatment of cancer-related hypercalcemia that is resistant to hydration.

Summary of Business and Research and Development Programs

Our goal is to establish Genta as a biopharmaceutical leader and preferred partner in the oncology market and eventually, as direct marketers of our products in the United States. Our key strategies in this regard are:

- Build on our core competitive strength of oncology development expertise to establish a leadership position in providing biopharmaceutical products for the treatment of cancer.

- Expand our pipeline of products in two therapeutic categories, DNA/RNA Medicines and Small Molecules, through internal development, licensing and acquisitions.

- Accelerate development of our pipeline product therapeutic candidates, including tesetaxel and oral gallium-containing compounds, into later stages of clinical development.

- Establish our lead antisense compound, Genasense ® , as the preferred chemosensitizing drug for use in combination with melanoma and other cancers; and

- Establish a sales and marketing presence in the U.S. oncology market.

Research and Development Programs

DNA/RNA Medicines

A number of technologies have been developed using modifications of DNA or RNA. These agents have been used as scientific tools for laboratory use to identify gene function, as diagnostic probes to evaluate diseases, and — more recently — as potential drugs to treat human diseases. Collectively, these technologies include methods known as antisense, RNA interference, micro-RNA, decoys and gene therapy. Founded in 1988, Genta was one of the first companies established to exploit these new technologies for use as potential drugs and we remain broadly committed to research and development of these compounds with a specific focus on cancer medicine, commonly known as oncology. Our most advanced drugs in our DNA/RNA Medicines program involve the use of antisense technology.

Antisense Technology

Most cellular functions, including whether cells live or die, are carried out by proteins. The genetic code for a protein is contained in DNA, which is made up of bases known as nucleotides that are arranged in a specific sequence. The specificity of the sequence accounts for the production of a specific protein. In order for DNA to produce a protein, an intermediate step is required. In this step, DNA is transcribed into messenger RNA, or mRNA. The sequence of mRNA that encodes a protein is oriented in only one direction, which is known as the “sense” orientation.

Antisense drugs are short sequences of chemically modified DNA bases that are called oligonucleotides, or oligos. The oligos are engineered in a sequence that is exactly opposite (hence "anti") to the "sense" coding orientation of mRNA. Because antisense drugs bind only short regions of the mRNA (rather than the whole message itself), they contain far fewer nucleotides than the whole gene. Moreover, since they are engineered to bind only to the matching sequence on a specific mRNA, antisense drugs have both high selectivity and specificity, which can be used to attack production of a single, disease-causing protein. Genasense ® is an antisense oligo that is designed to block the production of Bcl-2.

We have devoted significant resources towards the development of antisense oligos that contain a phosphorothioate backbone, which is the nucleotide chain comprised of ribose and phosphate groups. However, we also have patents and technologies covering later generation technologies that involve mixed backbone structures, as well as sterically fixed chemical bonds, that may further enhance the molecule's ability to bind to the intended target. Moreover, we have developed certain formulations that can be used to more efficiently increase the uptake of oligos into cells. Some of these advanced technologies may be incorporated into future products from our DNA/RNA Medicines program.

Genasense ® as a Regulator of Apoptosis ("Programmed Cell Death")

The programmed death of cells, also known as apoptosis, is necessary to accommodate the billions of new cells that are produced daily and also to eliminate aged or damaged cells. However, abnormal regulation of the apoptotic process can result in disease.

Cancer is commonly associated with the over- or under-production of many types of proteins. These proteins may be directly cancer-causing (i.e., "oncogenic") or they may contribute to the malignant nature of cancer (for instance, by increasing the longevity of cancer cells or making them more likely to spread throughout the body). The ability to selectively halt the production of certain proteins may make the treatment of certain diseases more effective. Apoptosis is regulated by a large number of proteins, particularly members of the Bcl-2 protein family. In an effort to make existing cancer therapy more effective, we are developing Genasense ® to target and block the production of Bcl-2, a protein that is central to the process of apoptosis.

Bcl-2 as an Inhibitor of Programmed Cell Death

Normally, when a cancer cell is exposed to treatment, such as with chemotherapy, radiation or immunotherapy, a "death signal" is sent to an organelle within the cell called the mitochondrion. The mitochondrion then releases a factor known as cytochrome C that activates a series of enzymes called caspases. These enzymes cause widespread fragmentation of cellular proteins and DNA, which ultimately causes cell death.

Bcl-2 is normally found in the mitochondrial membrane where it regulates the release of cytochrome C. High levels of Bcl-2 are associated with most types of human cancer, including major hematologic cancers such as lymphomas, myeloma, and leukemia, and solid tumors such as melanoma and cancers of the lung, colon, breast and prostate. In these diseases, Bcl-2 inhibits the release of cytochrome C that would ordinarily be triggered by cancer therapy. Thus, Bcl-2 appears to be a major contributor to both inherent and acquired resistance to cancer treatments. Overcoming resistance to chemotherapy poses a major challenge for cancer treatment.

In cancer cells, Bcl-2 inhibits the process of programmed cell death, thereby allowing cells to survive for much longer than normal cells. Genasense