DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Diann Nagami
Director, Regulatory Affairs
Pharmacyclics, Inc.
995 East Arques Avenue
Sunnyvale, CA 94085-4521

RE: IND #[ ]
Xcytrin® (motexafin gadolinium) Injection
MACMIS # 10164

Dear Ms. Nagami:

This letter notifies Pharmacyclics, Inc. (Pharmacyclics) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, Pharmacyclics promoting its investigational new drug, Xcytrin, as safe or effective on its website www.pcyc.com and through promotional activities at their commercial exhibit booth at the 37th American Society of Clinical Oncology (ASCO) Annual Meeting held in San Francisco, California in May 2001. Our specific objections follow:

Promotion of an Investigational Drug

A sponsor shall not represent, in a promotional context, that an investigational drug is safe or effective for the purpose under investigation. Pharmacyclics makes numerous claims regarding the safety and efficacy of Xcytrin on its website. These claims are based solely upon preliminary and inconclusive data since the clinical investigations of Xcytrin are in the initial stages. Following are selected statements from the website that promote Xcytrin as safe or effective:

> "Pre-clinical and clinical data indicate that Xcytrin, after repeated injections, accumulates selectively in tumors and increases the vulnerability of cancer cells to the damaging effects of radiation or chemotherapy."
>
> "These products represent a new class of drugs - rationally designed, porphyrin-like molecules, called texaphyrins, that are capable of upsetting the intracellular oxidation-reduction balance and disrupting the bioenergetic process in diseased tissue, such as cancer, atherosclerosis and retinal tissue."
>
> "Combination treatment with texaphyrins and various forms of energy (e.g., ionizing radiation, chemotherapy or light) may be capable of reducing or eliminating diseased tissue."

"This ability to capture free electrons has allowed for these complexes to be developed to enhance the effects of radiation and chemotherapy for cancer, as well as treatments for heart and vascular disease and retinal diseases."

"Texaphyrin treatment weakens the tumor cells and renders them more vulnerable to attack by other therapies such as and chemotherapy."

"Texaphyrins selectively enhance tumor cell responsiveness to other therapies such as ionizing radiation and chemotherapy."

"The ability of texaphyrins to localize in tumors and atherosclerotic plaque lesions make these compounds extremely effective for photodynamic therapy of cancer and cardiovascular disease."

In addition, Pharmacyclics provides a video under the heading "See how we believe Xcytrin could work" the on the Xcytrin webpage. This video contains an animation showing human brain tumors shrinking then disappearing following Xcytrin therapy.

Furthermore, in the commercial exhibit booth of the 2001 ASCO Meeting, Pharmacyclics' representative disseminated a promotional pamphlet[1] and highlighted several claims regarding the safety and efficacy of Xcytrin that were similar to those mentioned above.

Therefore, the website and promotional activities at the 2001 ASCO Meeting are in violation of the Act and its implementing regulations because Pharmacyclics promoted an investigational new drug as safe or effective for uses under investigation. These comments should also be applied to representations of other investigational agents on this website.

Requested Action

Pharmacyclics should immediately cease making the claims described above and other promotional activities or materials for Xcytrin that make the same or similar claims or presentations. Pharmacyclics should submit a written response to DDMAC on or before July 18, 2001, describing its intent and plans to comply with the above. In its letter to DDMAC, Pharmacyclics should include the date on which this and other similarly violative materials were discontinued.

Pharmacyclics should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence

[1] Pamphlet PM-004-01-R1 PCYC-001 entitled "Think Radically. Act Selectively"

regarding this matter, please refer to MACMIS ID # 10164 in addition to the NDA number. DDMAC reminds Pharmacyclics that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Grillo
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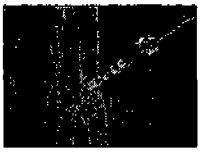

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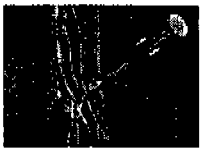

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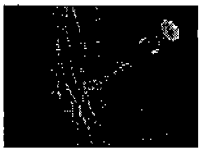

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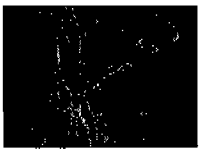

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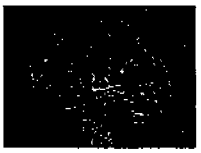

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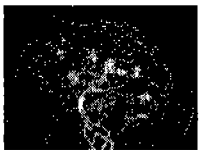

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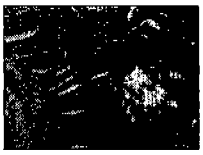

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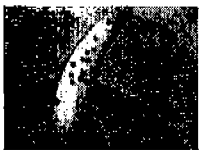

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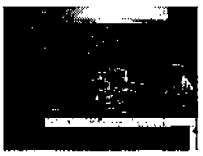

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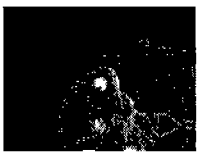

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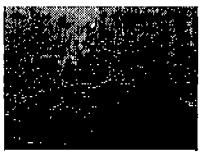

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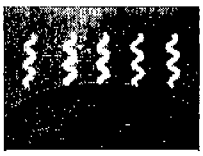

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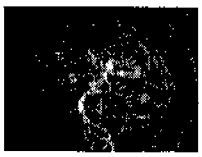

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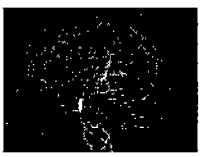

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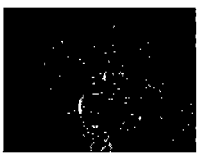

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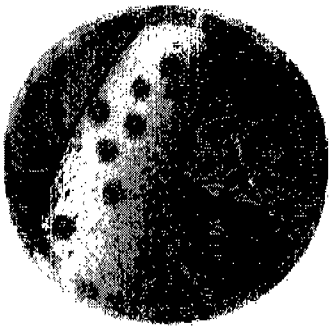
Pipeline
Xcytrin®
Lutrin®
Antrin®
Optrin™
Clinical Trials

Diverse Products



Pharmacyclics' pipeline of products is based on a unique technology platform. These products represent a new class of drugs - rationally designed, porphyrin-like molecules, called texaphyrins, that are capable of upsetting the intracellular oxidation-reduction balance and disrupting the bioenergetic process in diseased tissue, such as cancer, atherosclerosis and retinal tissue. Combination treatment with texaphyrins and various forms of energy (e.g., ionizing radiation, chemotherapy or light) may be capable of reducing or eliminating diseased tissue. A more detailed explanation of the mechanism of action of texaphyrins is provided in the Technology section of this web site.

The company's lead product candidates are Xcytrin® (motexafin gadolinium) Injection, a gadolinium texaphyrin drug being developed for potential use with radiation and/or chemotherapy for the treatment of cancer; Lutrin® (motexafin lutetium) Injection, a lutetium texaphyrin drug for potential use in the photodynamic therapy (PDT) of cancer; Antrin® (motexafin lutetium) Injection, a lutetium texaphyrin drug for potential use in photoangioplasty of atherosclerosis, i.e. peripheral arterial and coronary artery disease; and Optrin™ (motexafin lutetium) Injection, a lutetium texaphyrin molecule for potential use in the photodynamic therapy of ophthalmic diseases, such as age-related macular degeneration.

Pharmacyclics has retained worldwide marketing rights to Xcytrin, Lutrin and Antrin, and has partnered with Alcon, one of the world's leading ophthalmology companies, to develop and market Optrin worldwide.

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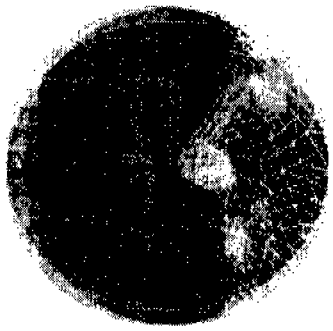
Versatile Technology

Porphyrins
Texaphyrins



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Pharmacyclics' technology platform is based on a novel class of rationally designed porphyrin-like compounds, called texaphyrins. In nature, porphyrins, such as vitamin B_{12}, clorophyl and heme, are involved in energy production and metabolism and are critical to life. For example, vitamin B_{12} enables the synthesis of protein and DNA, and chlorphyl is involved in converting light energy into chemical energy in a process known as photosynthesis.

Texaphyrins are designed to provide a valuable new therapeutic approach to a variety of diseases. Of particular importance are two key properties: texaphyrins selectively target diseased tissue and they have a very high affinity for electrons (even higher than natural porphyrins do). Texaphyrins selectively penetrate and are retained in tumor cells and certain other diseased cells. Intracellularly, texaphyrins are very active as reduction oxidation (redox) modulators.

Porphyrins
Texaphyrins

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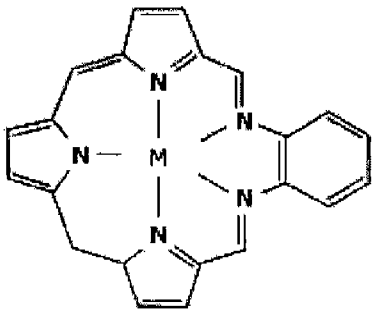
Texaphyrins

Invention Of Texaphyrins

None of the previously created expanded porphyrin systems formed stable complexes with large metal cations such as the lanthanides until the invention of the texaphyrins (Texas-size porphyrins). First published in 1988, texaphyrins are a novel class of molecules created by Professor Jonathan Sessler and coworkers at the University of Texas at Austin. An exclusive, worldwide license to this technology has been granted to Pharmacyclics, Inc. The company holds many patents covering composition of matter, use, and synthesis for a number of Pharmacyclics' texaphyrin compounds. To date, texaphyrins remain the only family of expanded porphyrins undergoing clinical development that retain many of the properties of naturally occurring porphyrins, including formation of planar, aromatic, 1:1 stoichiometric complexes with metal cations; selective biolocalization (texaphyrins have been shown to selectively localize within the cells of certain tissues and organs such as cancerous tumors, atherosclerotic plaque, and the liver); and energy transfer capabilities.

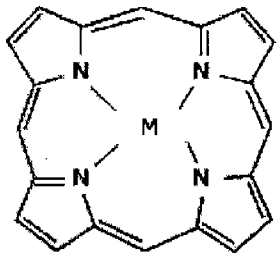


M=Metal Ion

Metallotexaphyrin

Unique Covalent Binding of Metal Ions

Relative to the naturally occurring porphyrin structure, texaphyrins possess a 20 % larger binding cavity with five (rather than four) nitrogen donor atoms. These ligands create stable, non-labile n-5 complexes with large cations such as cadmium(II), mercury(II), indium(III), yttrium(III), and lanthanum(III).(5b, 7) Of particular interest are metallotexaphyrin complexes formed from metals of the lanthanide series. The 1:1 texaphyrin-to-metal stoichiometry and pentadentate coordination via the delocalized pi-electron network has been confirmed by single crystal X-ray structure determinations, of which approximately a dozen have been published. The metal ion is held within the texaphyrin plane and is positioned nearly symmetrically in the center of the ring. The equatorial binding allows for free interaction of the axial poles of the metal with other molecules. This is especially important for lanthanide metals, that bind readily dissociable ligands such as chloride, acetate, and nitrate in order to achieve coordinative saturation and balance charge.



M=Metal Ion

Metalloporphyrin

The versatility of this approach lies in the ability to prepare a variety of compounds through permutations in one or more of the subunits. To date, over 100 metallotexaphyrin compounds have been prepared. The synthetic flexibility makes it possible to modify functional groups on the periphery of the texaphyrin ring in order to alter chemical and biological properties. Insertion of the metal ion in the final step of the synthesis also greatly simplifies the preparation of a wide range of metallotexaphyrins.

Texaphyrins Are Extremely Electron Affinic
The extended pi-system of texaphyrins also influences their electron affinity properties. These molecules can undergo one electron reduction to form stable pi-radical cations. This ability to capture free electrons has allowed for these complexes to be developed to enhance the effects of radiation and chemotherapy for cancer, as well as treatments for heart and vascular disease and retinal diseases.

Texaphyrins Are Redox Modulators
Because texaphyrins are very efficient electron acceptors, they function as redox modulators in tumor cells. The repeated capture of an electron by a texaphyrin from cytoprotective reducing agents (antioxidants such as glutathione and ascorbate) and the catalytic transfer of the electron from reduced texaphyrin to oxygen have been termed "futile redox cycling."

Futile redox cycling disrupts the cellular bioenergetic processes and causes increased oxidative stress through the formation of reactive oxygen species. Texaphyrin treatment weakens the tumor cells and renders them more vulnerable to attack by other therapies such as radiation and chemotherapy.

Texaphyrin molecules steal electrons from intracellular reducing agents and transfer the electrons to oxygen to form reactive oxygen species (such as hydrogen peroxide) and free radicals. The futile redox cycling of texaphyrins depletes the resevoir of cytroprotective reducing agents and inhibits their function in cellular repair.

Making Tumor Cells More Vulnerable to Therapy
Texaphyrins selectively enhance tumor cell responsiveness to other therapies such as ionizing radiation and chemotherapy. Treatment of tumors with X-rays causes cell death through the production of inracellular free radicals and reactive oxygen species. The redox-modulating effect of texaphyrins selectively enhances the tumor cells' response to radiation therapy by compromising the natural defenses and repair processes of tumor cells.

The texaphyrins have unique advantages over previous agents designed to enhance radiation therapy in that they have the potential to destroy both oxic and radiation-resistant hypoxic tumor cells. The biolocalization properties of the texaphyrins provide additional advantages by enhancing the effects of radiation in the tumor more than in the surrounding normal tissue.

Other Potential Medical Applications
The unique structural and biolocalization properties of the metallotexaphyrins have led to a diversity of medical applications for which these molecules may be used. Synthetic modifications to the texaphyrin periphery can alter the water solubility and biolocalization properties. Selection of the appropriate metal provides the texaphyrin compound with the ability to perform desired functions such as transforming X-rays or laser light into forms of energy capable of producing localized tissue destruction.

One application of texaphyrins has been in photodynamic therapy. In this procedure, a light-absorbing dye or photosensitizer capable of

accumulating at the treatment site is irradiated with a specific frequency of visible light to produce excited state singlet oxygen. Singlet oxygen is extremely reactive with cellular components and results in cell death. Ideally, the photosensitizer absorbs in the 700 - 800 nanometer spectral region since photons of these wavelengths are able to penetrate deeply into tissues but are not absorbed by other pigments in the body. The aromatic 22 pi-electron delocalization of texaphyrins induces a red-shift in the Q-type absorption bands of the metallated complexes from the 600 - 650 nanometer range typical for porphyrins to the optimal range of 700 - 760 nanometers. Metallotexaphyrins incorporating diamagnetic metals (metals with no unpaired electrons) such as lutetium(III) are able to use the absorbed 700 - 760 nanometer photons to generate relatively long-lived triplet state complexes that efficiently generate cytotoxic singlet oxygen. The ability of texaphyrins to localize in tumors and atherosclerotic plaque lesions make these compounds extremely effective for photodynamic therapy of cancer and cardiovascular disease. Another application of the metallotexaphyrin photosensitizers is in regulating gene expression. These metallotexaphyrins can be attached to oligonucleotides to produce conjugates which are capable of photo-induced site-specific cleavage of DNA.

The accessibility of the metal ion apical sites also enables certain lanthanide(III) texaphyrins (where the lanthanide metals include europium, dysprosium, and terbium) to effect hydrolysis of phosphate diester bonds. An important application of this capability has been to hydrolyze or cleave phosphodiester bonds of RNA.(14) The stability of the metallotexaphyrin complexes not only makes it possible to direct the lanthanide metal ions to specific nucleotide sequences by attaching the complexes to oligomers that are complementary to the target sequences, but it also allows for the molecules to function in a catalytic manner. The ability to site-specifically cleave RNA, combined with the biolocalization properties of texaphyrins, makes these complexes potentially useful agents for therapy of a variety of diseases and disorders including cancer, certain viruses such as HIV and hepatitis, and other disorders such as autoimmune diseases.

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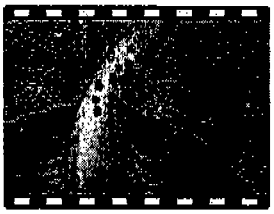
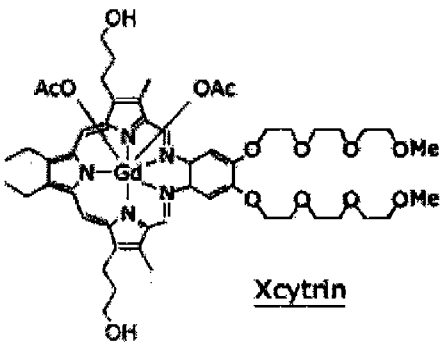


See how we believe Xcytrin® could work - download Quicktime (1.9 MB) Movie or RealVideo (.09 MB) File

Figure 1



Xcytrin

XCYTRIN®

Xcytrin® (motexafin gadolinium) Injection is a novel drug that augments the activity of radiation and chemotherapy via a unique mechanism of action. While chemotherapy and radiation therapy alone have been effective at treating cancer patients, they have many limitations, including harmful side effects due to non-selectivity and limited efficacy. Pre-clinical and clinical data indicate that Xcytrin, after repeated injections, accumulates selectively in tumors and increases the vulnerability of cancer cells to the damaging effects of radiation or chemotherapy.

Gadolinium Texaphyrins

Pharmacyclics is currently conducting a pivotal Phase III clinical trial with Xcytrin for the treatment of brain metastases, one of the most common conditions treated with radiation therapy. There are about 170,000 cases per year in the United States and the incidence is increasing. The most common causes of brain metastases are lung and breast cancer. Brain metastases occur when cancer cells spread to the brain and grow, causing major neurologic complications and, in many cases, death. Patients with brain metastases usually suffer serious deterioration of neurocognitive function such as loss of short-term memory, compromised verbal skills and fine motor coordination, and reduction in cognitive performance. Most patients with brain metastases have multiple lesions and are not candidates for surgical resection or radiosurgery. The goal of whole brain radiation therapy is to reverse or prevent neurological deterioration and prevent death due to tumor progression in the brain.

In addition to the Phase III brain metastases study, there are other studies now underway with Xcytrin. Under a cooperative research and development agreement with Pharmacyclics, the National Cancer Institute has also initiated clinical trials of Xcytrin for the treatment of primary brain tumors, non small-cell lung cancer, childhood gliomas (life-threatening brain tumors in children) and pancreatic cancer. Several other trials in other cancer types are in the planning stages, including a Phase II clinical trial in primary brain tumors that should begin in the first half of 2001.

Go to Xcytrin® Clinical Trials

There are no commercially available agents that enhance the effects of radiation or chemotherapy due primarily to the inability of agents tested to date to produce a differential effect between tumors and normal tissue and the difficulty in assessing when the maximum concentrations of the drugs have accumulated in neoplastic tissue. However, the market potential for a product that increases the effectiveness of radiation therapy for cancer patients alone could be substantial. Of the 1.4 million newly diagnosed patients with cancer each year in the U.S., approximately 50% will be treated with radiation therapy as part of their initial disease management, and approximately 150,000 additional patients with recurrent disease will receive radiation therapy.

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Pharmacyclics
Limiting Medicine
Therapeutics. Act Selectively.

Upsetting the Redox Balance of Tumor Cells

The "balanced" redox state of a tumor cell in the absence of texaphyrins is shown diagrammatically in Figure 4 (below).

The effects of texaphyrins on the redox state of a tumor cell are shown diagrammatically in Figure 5 (on adjacent page). Texaphyrin molecules "steal" electrons from intracellular reducing agents and transfer the electrons to oxygen to form reactive oxygen species (such as hydrogen peroxide) and free radicals. The futile redox cycling of texaphyrins depletes the energy stores of cancer cells as well as their reservoir of cytoprotective reducing agents—thus interfering with the cells' internal repair mechanisms.

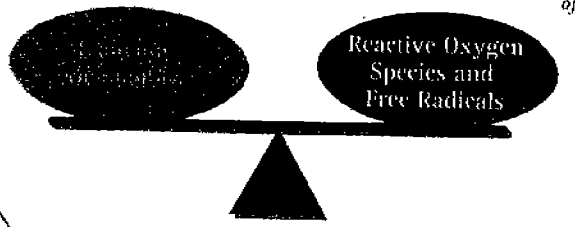


Figure 4. Diagram of the redox balance of tumor cells

Figure 5. Diagram of texaphyrins upsetting the redox balance of tumor cells

Making Tumor Cells More Vulnerable to Therapy

Texaphyrins may selectively enhance tumor cell responsiveness to other therapies such as ionizing radiation and chemotherapy. Treatment of tumors with X-rays causes cell death through the production of intracellular free radicals and reactive oxygen species. The redox-mediating effect of texaphyrins may selectively enhance tumor cells' response to radiation therapy by compromising the natural defenses and repair processes of tumor cells.

Exciting Pathways Designed to Selectively Destroy Cancer Cells

Texaphyrins selectively target and accumulate in tumor cells. Because texaphyrins are very efficient electron acceptors, they function as redox mediators in tumor cells. The repeated capture of an electron by a texaphyrin from cytoprotective reducing agents (antioxidants such as glutathione and ascorbate) and the catalytic transfer of the electron from reduced texaphyrin to oxygen have been termed "futile redox cycling."

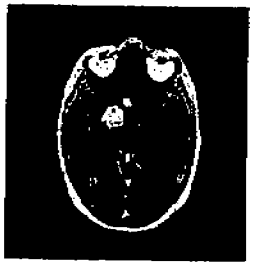
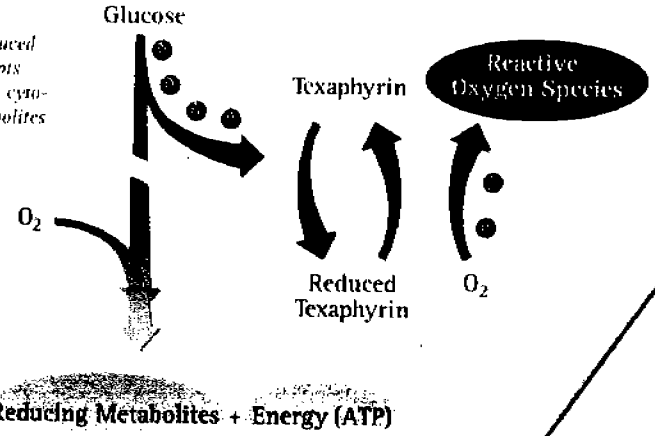


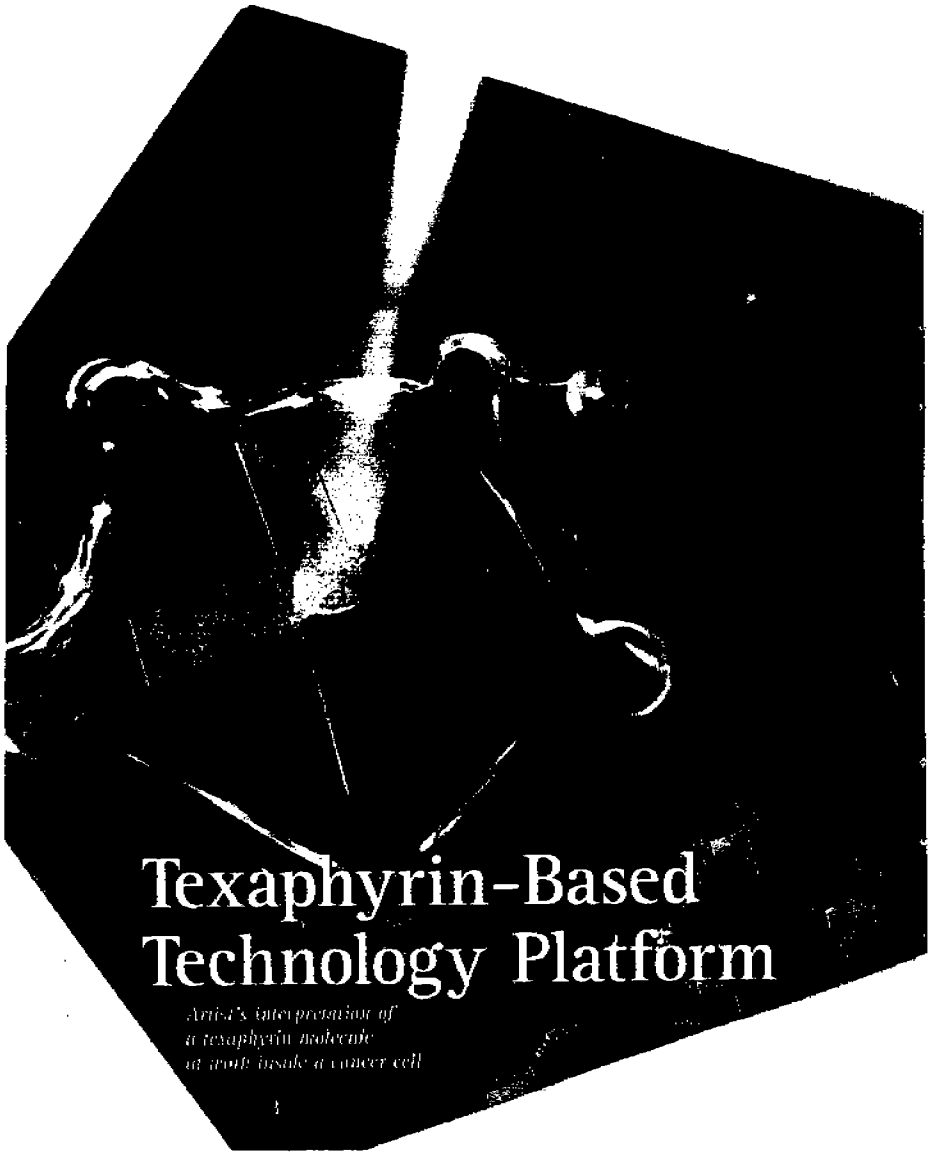
Figure 2. Selective uptake and retention of texaphyrin in brain metastases detectable by magnetic resonance imaging (MRI)

Futile redox cycling disrupts a cancer cell's energy metabolism and causes increased oxidative stress through the formation of reactive oxygen species, such as hydrogen peroxide. Texaphyrin treatment weakens the tumor cells, which may render them more vulnerable to attack by other therapies, such as ionizing radiation and chemotherapy.

Futile Redox Cycling

Figure 3. Texaphyrin-induced futile redox cycling disrupts a cell's ability to produce cytoprotective reducing metabolites and energy





Texaphyrin-Based Technology Platform

Artist's interpretation of a texaphyrin molecule in action inside a cancer cell

Pharmacyclics' technology platform is based on a novel class of rationally designed porphyrin-like biomolecules, called texaphyrins. In nature, porphyrins, such as vitamin B_{12}, chlorophyll, and heme, are involved in energy production and metabolism and are critical to life. For example, vitamin B_{12} enables the synthesis of proteins and DNA, and chlorophyll is involved in converting light energy into chemical energy in the process of photosynthesis.

As shown by the generalized chemical structure in Figure 1, texaphyrins are small, ring-shaped molecules containing a metal in the center.

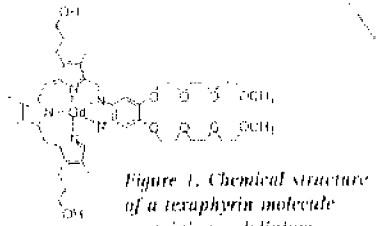
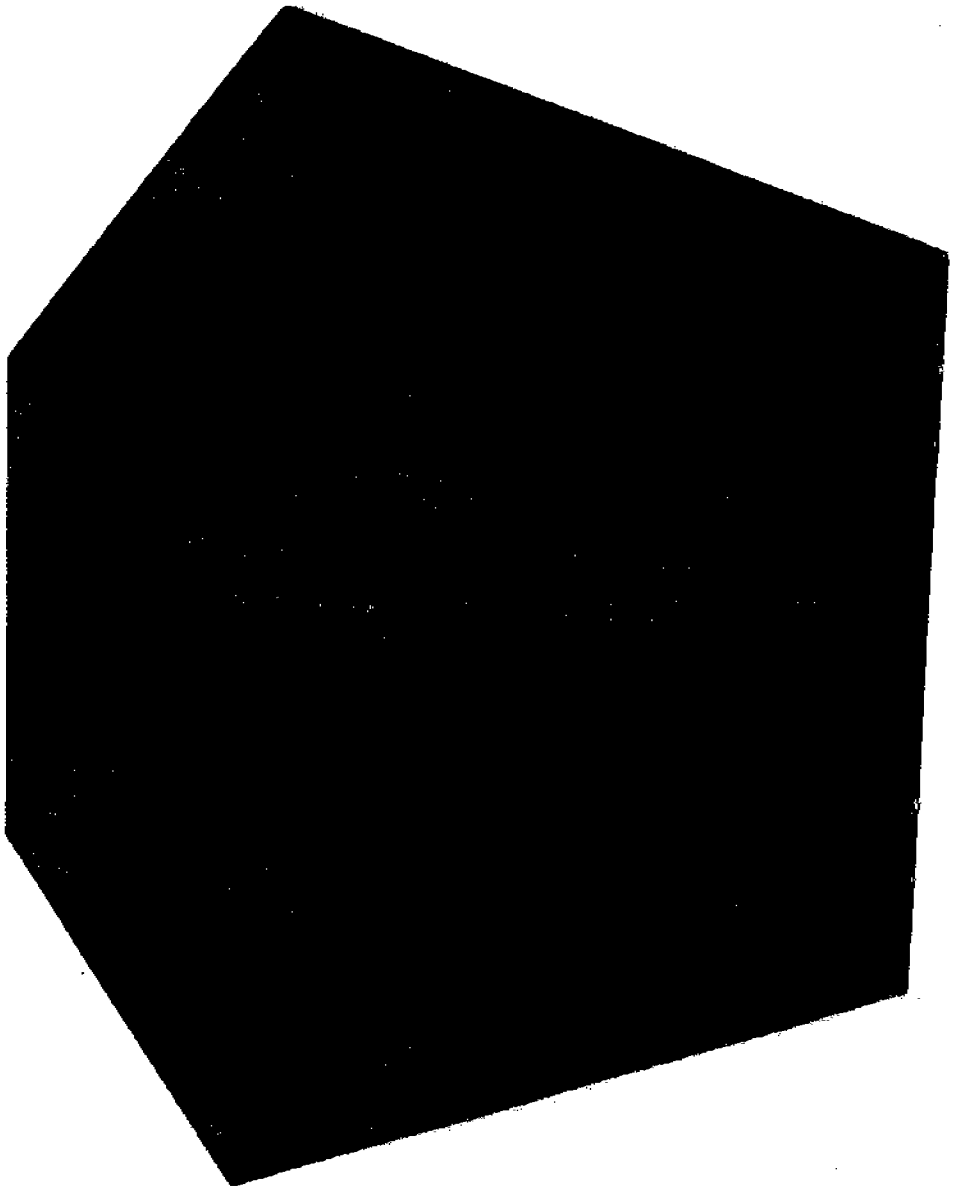


Figure 1. Chemical structure of a texaphyrin molecule containing gadolinium

Texaphyrins are designed to provide a valuable new therapeutic approach to a variety of diseases. Of particular importance are two key properties: texaphyrins selectively target diseased cells (based on metabolic differences compared to normal cells) and they have a very high affinity for electrons (even higher than natural porphyrins do). Texaphyrins selectively penetrate and are retained in tumor cells and certain other diseased cells. Intracellularly, texaphyrins are very active as oxidation-reduction (redox) mediators.



Pharmacyclics is committed to improving lives through the research and development of novel drugs that can improve the therapy of serious diseases, such as cancer and atherosclerosis.

Our pipeline of products is based on a unique technology platform. These products represent a new class of drugs—rationally designed, porphyrin-like biomolecules, called texaphyrins, that function as intracellular oxidation-reduction (redox) mediators, disrupting the energy metabolism and repair mechanisms of diseased cells. Texaphyrins may render tumor cells more vulnerable to cancer treatments. A more detailed explanation of the mechanism of action of texaphyrins is provided on pages 3–8.