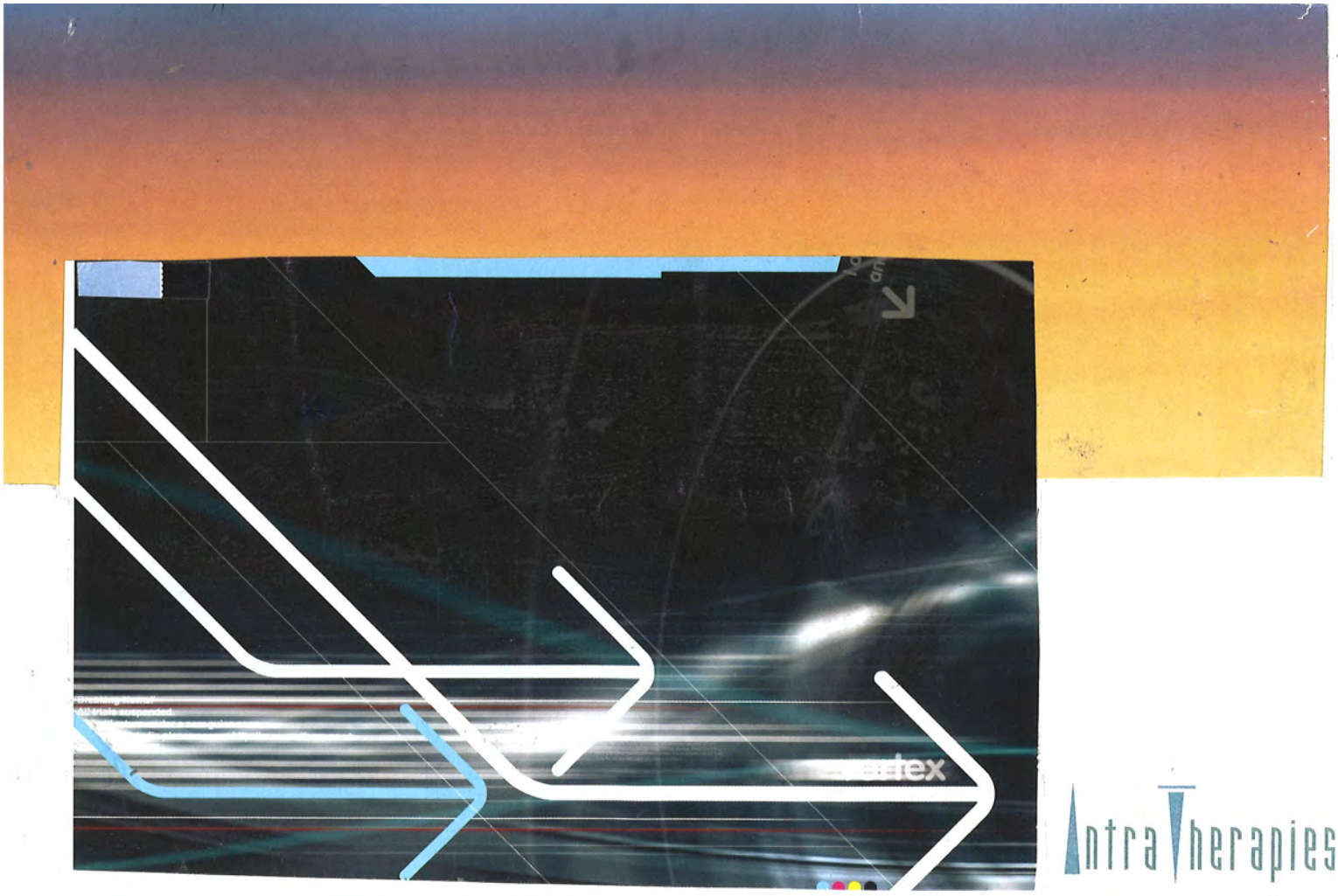
WORLD CANCER INSTITUTE



Antra Therapies

WORLD CANCER INSTITUTE

The Global Cancer Perspective:

The aging of populations, lifestyle changes in the developing world, together with significant advances in pharmacotherapy and diagnostics, will drive cancer treatment.

These new treatment options include:

- . Immunotherapies
- . Novel antineoplastic drugs.
- Epigenetics
- DNA Programmable Genetic Pharmacology

World Cancer Institute I HealthMedica

The World Cancer Institute is an affiliate of HealthMedica — a proactive health sciences group that views transformative medicine as the basis for transformative healthcare.

HealthMedica was founded by inventor / technologist, Nathan Sassover, whose cross-industry innovations have resulted in medical discoveries and therapeutic platforms addressing the neurobiology of aging as well as clinical developments based on molecular cancer genetics and DNA programmable genetic pharmacology.

His patented inventions and discoveries further extend to diverse technology venues ranging from micro-electronics to advanced Internet broadcast network architecture.

With a background that consistently demonstrates awareness of technology-driven opportunities before they are generally recognized, Nathan Sassover's leading edge innovations have created several industry sectors and unique market segments.

WORLD CANCER INSTITUTE

INTRODUCTION

The World Cancer Institute is a global forum and catalyst for worldwide dialogue and the advancement of clinically-validated and evidence-based treatment modalities directed toward the most challenging disease of our time. The Institute's primary objective is to enlarge the clinical framework and therapeutic possibilities resulting from the convergence of integrative cancer care conjoined with treatment programs which also have demonstrated promising indications in providing measurable, enhanced quality of life during treatment programs.

A New Perspective in Global Cancer Treatment

World Cancer Institute's global initiatives are directed toward advancing Oncology Clinical Protocols conjoining new cancer discoveries as pathway-specific monotherapies, with important new DNA targeting drugs based on molecular cancer genetics, Epigenetics, DNA programmable genetic pharmacology and other emerging integrative cancer therapies and immunotherapeutics.

World Cancer Institute's mandate for proactive care conjoins clinical objectives targeting a broader spectrum of balanced intervention and cancer preventive modalities during cancer treatment programs combined with the more informed use of biologic therapeutics for enhancing the body's internal restorative capacities to heal.

World Cancer Institute initiates proactive, leading edge oncologist reviewed processes and clinical assessment of diverse but clinically compatible integrative platforms. The resultant therapeutic programs and protocols target deeper systemic processes enabling the body's internal cellular restorative resources to intervene in the treatment regimen. These continuing objectives are directed toward advancing progressive treatment programs with clinically validated, evidenced-based outcomes targeting:

- Progression Free Survival (PFS)
- Overall Survival (O/S) inclusive of measurable enhanced Quality of Life (QOL) during treatment
- Reduction of traditional chemotherapy treatment side effects and toxicity in late stage cancers of all types. Driven by the dynamics of personalized medicine for optimal near and long term benefit, World Cancer Institute, and most all established and responsible medical institutions, recognize chemotherapy's clinically acknowledged and documented history of contributing to poor prognostic outcome which may often be the prime cause, or certainly a major factor, in the acceleration of overall physical, mental and emotional decline in a patient's condition within virtually all second, third and fourth line 'standard of care' chemotherapy treatment settings.

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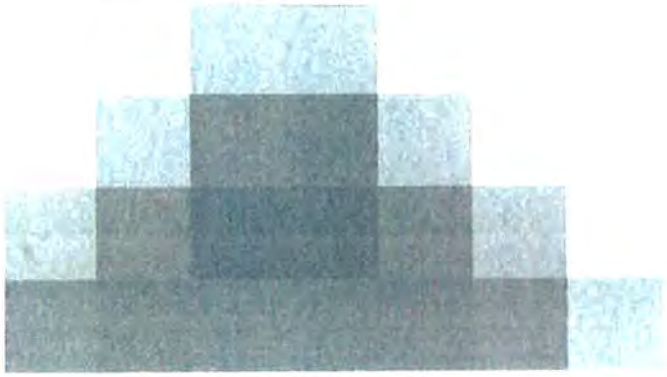
bioinnovation



IntraTherapies Institute

IECT

Epigenetic Cancer Therapeutics

Progression Free Survival (PFS) Overall Survival (O/S) Quality of Life (QoL)
IECT treatment programs

HEALTHMEDICA

IntraTherapies IECT

Epigenetic Cancer Therapeutics

During the past six years, commencing in 2008, IntraTherapies Institute has, in addition to its primary Neurosystemic Medicine platform, further pursued cancer research, specifically, molecular cancer genetics and epigenetic therapeutics.

Utilizing DNA programmable genetic pharmacology to inhibit the growth and replication of human cancer cells, IECT's hybrid clinical protocols and pathway-specific compounds are administered within the FDA compliant and recognized 'off label' mode as a monotherapy, or administered in conjunction with metronomic low dose chemotherapy.

The IECT Oncology Protocols are based on molecular cancer genetics and DNA programmable pharmaceutics (DNAPG) to inhibit the growth, replication and proliferation of human cancer cells.

IECT is a hybrid platform utilizing DNA Demethylation techniques conjoined with HDAC- histone deacetylase methyltransferase inhibitors with the clinical objective of optimal cellular function targeting the mitochondria and modulation of the mitotic spindle and microtubule interface.

The IECT primary mode of disease intervention targets epigenetic re-programming of gene expression adjacent to the primary DNA code. This enables gene silencing and gene reactivation within the alterable regions of the DNA which is independent of the DNA sequence. These programmable aspects of the human genome are pharmaceutically controllable and programmable for elimination of abnormal cell structures which may evolve over time to become various types of cancer. This integrative pathway-specific approach defines IECT-IntraTherapies Epigenetic Cancer Therapeutics.

IntraTherapies clinically validated results, based on radiology oncology reports, hematology laboratory data were obtained during an 8 week investigational study in Stage IIIB and Stage IV breast and colon cancer patients utilizing the IECT oncology treatment. The next phase of IntraTherapies oncology programs will be initiated across a broader patient population and extending to six solid tumor cancer categories as follows:

- Advanced (Stage III and IV) Breast Cancer
- Metastatic (Stage IV) Colon Cancer
- Metastatic (Stage IV) Castration-Resistant Prostate Cancer (CRPC)
- Advanced (Stage III and IV) Non Small Cell Lung Cancer (NSCLC)
- Advanced (Stage III and IV) Ovarian Cancer
- Metastatic (Stage IV) Renal Cell Carcinoma (Kidney Cancer)

Emerging independent clinical research in the area of HDAC- histone deacetylase inhibitors, one of several Intratherapies IECT therapeutic modalities referenced, is also exploring treatment potential for AML type leukemia.

IntraTherapies utilizes targeted combination therapies and pathway-specific drug compounds to achieve broader cancer interventional effect with enhanced safety at the cellular level, absent adverse impact on major cellular pathways, thereby resulting in reduction of treatment toxicity levels across six primary cancer categories. Although within a small patient group, the IECT conjunctive treatment approach has clinically demonstrated, during an eight week clinical investigational study, the ability to inhibit the growth, replication and proliferation of human cancer cells.

- IECT -Intratherapies Epigentic Cancer Therapeutics

Multi-Patient Investigational IECT treatment programs

Clinical Significance and Therapeutic Applications

The increasing degree of medical/scientific empirical evidence supporting thespecific pharmaceutical ingredients which comprise IntraTherapies Epigenetic Cancer Therapeutics (IECT) is based on independent research originating in numerous recognized medical/biological research centers in the US and Overseas, namely,- Indiana University School of Medicine; Indiana University Cancer Center – Departments of Surgery and Biochemistry/Molecular Biology and Walther Oncology Center; -Cancer Epigenetics Laboratory, Molecular Pathology Program, Spanish National Cancer Centre; -Osaka University Graduate School of Medicine – Japan.

Added to this scientific consensus, increasing clinical evidence and empirical data, published research about the specific chemical agents which are the primary active ingredients in all IntraTherapies Epigenetic Cancer Therapeutics compounds have appeared over the past several years in peer-reviewed and recognized clinical oncology journals such as:

- Cancer Research / American Association for Cancer Research;

-Current Opinion in Oncology, Journal of Pharmacological Sciences

-Elsevier Cancer Letters

-Molecular Cancer Therapeutics, Modern Pathology

-JNCI – Journal of the National Cancer Institute.

- Epigentic Cancer Therapeutics

These publications reaffirm and recognize the epigenetic compounds comprising IntraTherapies epigenetic cancer protocols as clinically and verifiably significant in controlling gene expression and cancer cell replication in oncology-based diseases.

Epigenetics refers to the function of DNA that does not depend on the coding DNA sequence itself but on the accessory molecules and mechanisms affected by DNA. It is known that epigenetic alterations are equally if not more important than classical genetic alterations to disrupt the function of tumor suppressor genes.

Scientists are increasingly recognizing that to understand human health and disease – not just what causes disease but how to prevent and reverse it – they need to know more than what kind of genes someone has, or what the DNA sequence of their genome is. Equally, if not more important, they need to know how cells use that genomic information. That is what epigenetics is all about: how genomic information encoded in the DNA sequence is regulated by other, non DNA-sequence external factors each of which plays a key role in gene expression by allowing or preventing transcription to proceed – that is, by turning genes on and off.

***These statements have not been evaluated by the FDA. These programs and products are not intended to diagnose, treat, cure or prevent any diseases.**

Intra Therapies

IECT

Intratherapies Epigenetic Cancer Therapeutics:

Background and Rationale

Epigenetics refers to the function of DNA that does not depend on the coding DNA sequence itself but on the accessory molecules and mechanisms affected by DNA. It is known that epigenetic alterations are equally if not more important than classical genetic alterations to disrupt the function of tumor suppressor genes.

The two most studied epigenetic aberrations common to all types of cancer are DNA hypermethylation and histone deacetylation, which cooperate to silence the expression of tumor suppressor genes, just as gene mutations and gene deletions do. The essential difference between these two alternative ways that tumor cells use to inactivate tumor suppressor genes is that, while the reversal of genetic alterations is technically almost unfeasible in clinical scenarios, the function of these epigenetically inactivated suppressor genes is easily reactivated by pharmacological means.

The Pharmacodynamics of Procaine and Parthenolide

Methylation-associated silencing of tumor suppressor genes is recognized as being a molecular hallmark of cancer. Procaine is a DNA methyltransferase inhibitor and in multiple studies has been shown to inhibit the growth of human cancer cells in vitro and in vivo. Parthenolide has also been shown to inhibit the growth of human cancer cells in vitro and in vivo.

Unlike genetic alterations, changes in DNA methylation are potentially reversible. This possibility has attracted considerable attention from a therapeutics standpoint.
Procaine and Parthenolide (IECT compound Proparthenolide) are non-nucleoside inhibitors of methyltransferases with reported anti-cancer and chemotherapy potentiating activity. Some identified pathways include but are not restricted to PTEN tumor suppressor gene, PI3K signalling pathway, and NF-KappaB.

Nucleoside-analogue inhibitors of DNA methyltransferases, such as 5-aza-2_-deoxycytidine, are able to demethylate DNA and restore silenced gene expression. Unfortunately, the clinical utility of these compounds has not yet been fully realized mainly because of their side effects. A few non-nucleoside inhibitors of DNA methyltransferases have been reported, including the anti-arrhythmia drug procainamide.

Following this need to find new demethylating agents, independent research has shown the cancer interventional potential of procaine, an anesthetic drug related to procainamide. As an example, within the MCF-7 prostate cancer cell line, it is known that procaine is a DNA-demethylating agent that produces a 40% reduction in 5-methylcytosine DNA content as determined by high-performance capillary electrophoresis or total DNA enzyme digestion.

Procaine can also demethylate densely hypermethylated CpG islands, such as those located in the promoter region of the *RAR_2* gene, restoring gene expression of epigenetically silenced genes. This property may be explained by findings that procaine binds to CpG-enriched DNA.

DMAPT

- Procaine and parthenolide in combination as pathway-specific compounds that have exhibited promising potential in vivo as cancer therapeutics.

- Cell division depends on the function of the mitotic spindle, which is composed of microtubules. The central role of the Microtubules has made them the target of several anticancer agents such as paclitaxel, docetaxel, and vinorelbine. Tubulin is the basic building block of the microtubules and tubulin cycles between a tyrosinated and detyrosinated form based on the activity of the opposing enzymes tubulin-tyrosine ligase (TTL) and tubulin carboxypeptidase (TCP). Cancer cells have a decrease in the level of TTL and accumulate high amounts of detyrosinated tubulin.
- Parthenolide is a TCP inhibitor and has been shown to decrease the level of tyrosinated tubulin in cancer cells; parthenolide has also been shown to inhibit the growth of human cancer cells in vitro and in vivo.
- Procaine also has growth-inhibitory effects in these cancer cells, causing mitotic arrest.

Thus, as pathway-specific compounds, procaine and parthenolide are promising agents for future cancer therapies based on epigenetics.

WORLD CANCER INSTITUTE

Selegiline

IECT Neurodegenerative Inhibitors- Neuro Regulating Compounds-

Quality of Life (QoL)Factors in late stage cancer treatment

Selegiline is a a selective and irreversible inhibitor of Monoamine oxidase type B inhibitor (MAO-B) with a primary effect in the regulation and stabilization of acetylcholine. Selegiline's function as an acetylcholinesterase inhibitor Selegiline provides collateral pharmacodynamic modulation of catacholemines, dopamine, serotonin and epinephrine.

Its use in the IECT protocols is based on QoL aspects, notably its mood regulating functions in mild to major clinical mood disorders ranging from depression to anxiolytic conditions which often are also present in patients presenting with chronic long term illnesses including cancer.

IECT- Selegiline

MAO-B Inhibitor Therapeutic Prevention of Mammary Tumor Development through NeuroImmuno Modulation in the Spleen and Lymph Nodes

BACKGROUND:

Development of mammary tumors is an age-associated phenomenon that is likely due to deficits in the neuroendocrine-immune interactions. Utilization of a monoamine oxidase-B (MAO-B) inhibitor, can enhance immune responses and restore noradrenergic (NA) innervation with carcinogen-induced and spontaneously developing mammary tumors.

OBJECTIVES:

Within a triangulated protocol comprised of compounds addressing DNA Methylation and HDAC- Histone Regulation, an MAO-B inhibitor, as a monotherapy or combined with the 2 noted compounds, prevented the spontaneous development of mammary tumors accompanied by restoration of immunity in the spleen and draining lymph nodes (DLN) and sympathetic NA innervation in the spleen and (2) clinically validate that an MAOB inhibitor can influence the proliferation of estrogen receptor (ER)- positive (MCF-7 and T47D) and ER-negative (MDA-MB-231 and Hs 578T) human breast cancer cells.

METHODS:

Cells of ER-positive (ER+) and ER-negative (ER-) human breast cancer cell lines were targeted with the MAO-B Inhibitor conjoined with an DNA Demethylation compound during an 8 week therapeutic program in a Stage 3B-IBC- to examine the proliferation of cells.

RESULTS:

In the validated presence of Tumor incidence increase, MAO-B as monotherapy or more significantly, as a combination therapy treatment significantly reduced the incidence of mammary tumors in a 52 year old female patient.

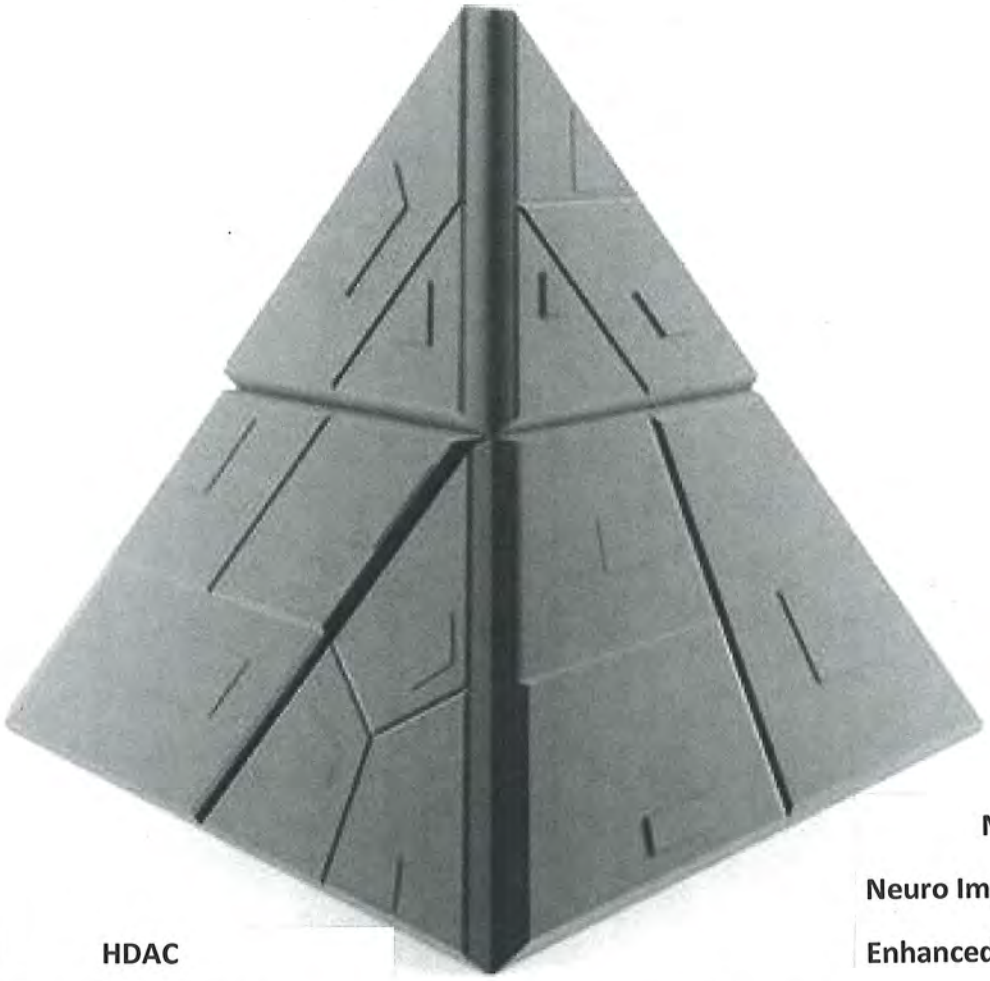
Treatment with MAO-B enhanced IL-2 and IFN-γ production in both the spleen and DLN as well as splenic natural killer (NK) cell activity. The MAO-B treatment, as monotherapy, also increased concanavalin A (Con A)-induced proliferation of T lymphocytes in the DLN. MAO-B induced changes in immune responses were accompanied by enhanced NA innervation and NE content in the spleen. In vitro incubation of various concentrations of deprenyl with ER+ human breast cancer cell lines partly inhibited the proliferatio ' of cells, while it had no effect on the ER- breast cancer cells.

CONCLUSIONS:

These results suggest that (1) development of mammary tumors is mediated through the loss of immunity and sympathetic NA nerve fibers accompanied by reduced NE levels in the spleen, (2) the prevention of mammary tumor development by use of an MAO-B may involve the reversal of the tumor-associated decline in sympathetic NA activity and cell-mediated immune responses in the spleen and DLN and (3) the antitumor effects and MOA of the MAO-B may be partially mediated through ER-dependent intracellular signaling pathways.

DNA

Demethylation



HDAC

Histone Regulation

Via

Histone Deacetylase

Methyltransferase Inhibitors

NIM

Neuro Immuno Modulation

Enhanced Immuno Responses/

Restores Noradrenergic (NA) Innervation with

Mitigating Carcinogen–Induced spontaneous

Mammary Tumor Development

IECT: Intratherapies Epigenetic Cancer Therapeutics

An Oncology Treatment Program Utilizing DNA Programmable Genetic Pharmacology and Pathway-Specific DNA Demethylation Techniques for Inhibiting the Growth, Replication and Proliferation of Human Cancer Cells, Generally Administered as a Monotherapy or Conjunctively with Metronomic Low Dose Chemotherapy and other Oncologic, Surgical or Integrative Cancer Modalities

IntraTherapies Institute
Medical Advisor - Cancer Therapeutics | **Brent F.G. Treiger MD**

Interpreting Radiologist	Kelvin McDanuiel MD	Slidell Memorial Hospital
Interpreting Radiologist	Kishore V. Kamath MD	Slidell Memorial Hospital
Proxy Radiologist	Richelle C Lignon MD	Slidell Memorial Hospital

Clinical Protocol IECT Trivalent Compound Developer Nathan Sassover

IntraTherapies Epigenetic Cancer Therapeutics™ (IECT)

A Treatment Protocol Based on Molecular Cancer Genetics and DNA Programmable Genetic Pharmacology To Inhibit the Growth and Replication of Human Cancer Cells

Multi Site Clinical Investigational Studies in 6 Solid Tumor Cancer Categories

Response Rate / Progression Free Survival (PFS) / Overall Survival (OS) and Quality of Life (QOL) **Phase II** Investigational Studies in Patients with **Advanced (Stage III and IV) Breast Cancer**
Mode: IECT / Metronomic Chemotherapy

- Response Rate / Progression Free Survival (PFS) / Overall Survival (OS) and Quality of Life (QOL) **Phase II** Investigational Studies in Patients with **Metastatic (Stage IV) Colon Cancer**
  Mode: IECT / Metronomic Chemotherapy
- Response Rate / Progression Free Survival (PFS) / Overall Survival (OS) and Quality of Life (QOL) **Phase II** Investigational Studies in Patients with **Metastatic (Stage IV) Castration-Resistant Prostate Cancer (CRPC)**
  Mode: IECT / Metronomic Chemotherapy
- Response Rate / Progression Free Survival (PFS) / Overall Survival (OS) and Quality of Life (QOL)) **Phase II** Investigational Studies in Patients with **Advanced (Stage III and IV) Non Small Cell Lung Cancer (NSCLC)**
- **Mode: IECT Monotherapy**
- Response Rate / Progression Free Survival (PFS) / Overall Survival (OS) and Quality of Life (QOL) **Phase II** Investigational Studies in Patients with **Advanced (Stage III and IV) Ovarian Cancer**
  Mode: IECT Monotherapy
- Response Rate / Progression Free Survival (PFS) / Overall Survival (OS) and Quality of Life (QOL) **Phase II** Investigational Studies in Patients with **Metastatic (Stage IV) Renal Cell Carcinoma (Kidney Cancer)**
  Mode: IECT Monotherapy

IECT: Intratherapies Epigenetic Cancer Therapeutics

A Clinical Protocol based on molecular cancer genetics and DNA programmable genetic pharmacology to inhibit the growth and replication of human cancer cells.

Subject: -Medical Advisor-

IntraTherapies Institute
Medical Advisor - Cancer Therapeutics

Brent Treiger MD

Brent Treiger, M.D., is an internationally recognized clinical research oncologist and scientist with over fifteen years of product development experience in the biotech / pharmaceutical industry and has been significantly involved in the successful development of several oncology products. Among his drug discoveries is Doxal, one of the most globally recognized drugs for advanced ovarian cancer.

Based on his assessment of the clinical laboratory and radiology confirmed outcomes of treatment on advanced breast cancer and advanced colon cancer patients, who were treated with the Nathan Sassover' DNA Programmable Genetic Pharmacology clinical protocols, Dr Treiger concluded that Mr. Sassover's discoveries in molecular cancer genetics were a significant advancement within the new range of epigenetic therapeutics being introduced for advanced cancers. Specifically the notable absence of side effects combined with rapid onset of drug efficacy of the Sassover IECT oncology treatment protocols convinced Dr Treiger of the significant potential of the IECT approach to chemo-resistant cancers in six solid tumor categories and two hematologic malignancies, MDS- myelodysplastic syndrome and leukemia.

Dr. Treiger has joined as Medical Advisor to Intratherapies Institute, which was founded by Nathan Sassover in 2001, to create the wide scale treatment administration framework for Nathan Sassover's IECT --Intratherapies Epigenetic Cancer Therapeutics clinical protocols.

Dr. Treiger's unique clinical skills include assessment of clinical trials for likelihood of success, evaluating potential markets for new technologies, to identify the best opportunities for clinical development; devising strategies (clinical development plans) to achieve rapid regulatory approval and commercial success; long term experience interacting with the FDA; and designing and conducting clinical trials (Phase I – IV).

For multiple products, Dr. Treiger has designed Phase 1 programs, negotiated with the FDA at Pre-IND meetings, and prepared IND submissions, all of which have been approved on the first pass.

In addition, Dr. Treiger has developed novel regulatory strategies for multiple products and obtained FDA approval at End of Phase / Pre-Phase 3 meetings.

His responsibilities have included formulating global clinical development plans; writing protocols and monitoring clinical trials; and managing the clinical research department. He has experience in presenting to and successfully negotiating with corporate partners and with the FDA (CDER and CBER). Dr. Treiger's previous experience includes being on the faculty at the UCLA School of Medicine, running a successful private practice, and conducting multiple industry-sponsored clinical trials. Brent Treiger received his MD from Northwestern University Medical School and has authored numerous journal articles, book chapters and abstracts, and has delivered a wide range of presentations nationally.

EPIGENETIC THERAPEUTICS IN THE TREATMENT OF CANCER

ABSTRACT

Methods for the treatment of cancer in a patient using pharmaceutical compositions that regulate and modulate epigenetic pathways are disclosed.

RESEARCH

Clinical Protocol IECT Trivalent Compound

Developer **Nathan Sassover** **World Cancer Institute**

IntraTherapies Inc.
IntraTherapies Institute

Application No.:
Docket No.: 674443000100
Inventor: Nathan SASSOVER
Title: EPIGENETIC THERAPEUTICS IN THE TREATMENT OF CANCER

EPIGENETIC THERAPEUTICS IN THE TREATMENT OF CANCER

Nathan Sassover

Application No.:
Docket No.: 674443000100
Inventor: Nathan SASSOVER
Title: EPIGENETIC THERAPEUTICS
IN THE TREATMENT OF CANCER

FIELD

[0001] The invention relates generally to targeting epigenetic pathways to treat cancer in a patient.

BACKGROUND

[0002] For decades, it has been generally thought that cancer was solely caused by irreversible damage to some critical stretch of DNA within the genome. Research over the last 30 years has established the role of oncogenes and tumor-suppressor genes in malignant cell transformation. Recently, it has become apparent that epigenetic modifications are also central to the pathogenesis of cancer. Basic concepts of epigenetics and gene regulation are now recognized as central factors affecting cancer development. Knowledge of the epigenetic factors involved in cancer is also being applied in cancer research, diagnostics, and therapeutics. Unlike genetic damage, epigenetic changes can be reversed. Cancer treatments that reverse cancer-inducing epigenetic changes can be less toxic to a patient than conventional chemotherapy drugs.

[0003] One major drawback of chemotherapy drugs is that they are only effective for a small percentage of cancers. For the vast majority of cancers, however, chemotherapy drugs are not effective at improving survival. It is a statistical fact that second, third and fourth line chemotherapy treatment in almost all solid tumor and hematologic malignancies yields continuing diminishing efficacy in inhibiting cancer cell growth, replication and proliferation.

[0004] Furthermore, chemotherapy drugs are often not able to eliminate all cancer cells, which can lead to the development of cancer cells resistant to the drugs. The generation of drug-resistant cancer cells is a side effect of the high doses of drugs that are generally used in chemotherapy.

[0005] Another drawback of chemotherapy drugs is their toxicity. Many chemotherapy drugs target rapidly dividing cells, which include both cancer cells and normal cells.

FDA Approved Drug	Vorinostat	Decitabine	Azacitidine
Brand Name	Zolinza	Dacogen	Vidaza
Company	Merck	Eisai	Celegene
Epigenetic Target	HDAC inhibitor	Methylation inhibitor	Methylation inhibitor
Reported Side Effects	Diarrhea, fatigue, nausea, dysgeusia, thrombocytopenia, anorexia, decreased weight, muscle spasms, cholecystitis, deep vein thrombosis, enterococcal infection, exfoliative dermatitis, GI hemorrhage, infection, lobar pneumonia, myocardial infarction, ischemic stroke, pelviureteric obstruction, sepsis, spinal cord injury, streptococcal bacteremia, syncope, T-cell lymphoma, and ureteric obstruction.	Constipation, cough, diarrhea, dizziness, hair loss, headache, joint or muscle pain, loss of appetite, nausea, stomach pain or upset, trouble sleeping, vomiting, neutropenia, and thrombocytopenia, anemia, and pyrexia.	Fever, chills, weakness, dizziness, chest pain, myalgia, malaise, nausea, vomiting, constipation, diarrhea, anemia, neutropenia, febrile neutropenia, thrombocytopenia, hypokalemia, redness of the skin at the injection site, bruising of the skin at the injection site, injection site reaction, and small reddish-purple spots on the body.

FIG. 1

Patient AMJ

Case Overview: Feb 2008-

Patient AMJ is a 51year old white female diagnosed with breast cancer, left side, in February 2008. Infiltrating ductal carcinoma, Grade III, with extensive vascular invasion was observed in a needle core biopsy of a left breast mass. The cancer was ER(-) / PR(-), HER-2 IHC (2+) / FISH (-). A FNA of left axillary lymph nodes was consistent with metastatic adenocarcinoma of the breast and a punch biospsy of the left breast skin showed no evidence of carcinoma. Patient was self treating with botanical remedies and proper nutrition until she consulted with our clinic on October 9, 2008.

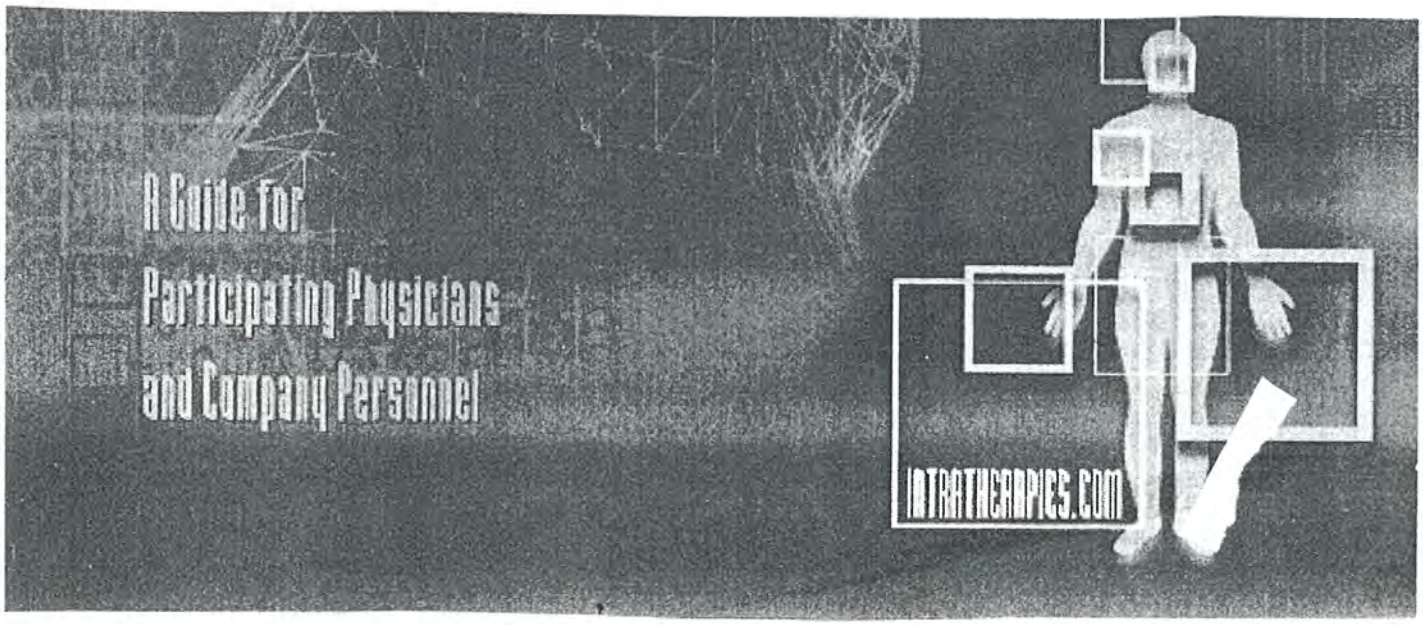
Interpreting Radiologist	**Kelvin McDanuiel MD**
Interpreting Radiologist	**Kishore V. Kamath MD**
Proxy Radiologist	**Richelle C Lignon MD**

IntraTherapies

WorldCancerInstitute

Breast Cancer: Patient Case Study

Eight Week Investigational



The following outlines a Clinical Investigational Study in one Stage III B Advanced Breast Cancer Patient. The patient history and treatment details are provided below.

IECT: Intratherapies Epigenetic Cancer Therapeutics

A Clinical Protocol based on molecular cancer genetics and DNA programmable genetic pharmacology to inhibit the growth and replication of human cancer cells.

The case history is based on a summary provided by the treating physician and then expanded upon with inclusion of the entire patient history and medical charts as conveyed by the treating physician in this study. The patient also reviewed the information and attests to the accuracy of the dates of treatment.

Patient AMJ

Patient AMJ is a 51 year old white female diagnosed with breast cancer, left side, in February 2008. Infiltrating ductal carcinoma, Grade III, with extensive vascular invasion was observed in a needle core biopsy of a left breast mass. The cancer was ER(-) / PR(-), HER-2 IHC (2+) / FISH (-). A FNA of left axillary lymph nodes was consistent with metastatic adenocarcinoma of the breast and a punch biospsy of the left breast skin showed no evidence of carcinoma. Patient was self treating with botanical remedies and proper nutrition until she consulted with our clinic on October 9, 2008.

On examination the entire left breast was invaded by the tumor. The center of the breast around the nipple was indurated, inflamed, and necrotic. The nipple was hardly distinguishable due to swelling and surrounding necrotic tissue. At least 25% of the left breast tissue surrounding the nipple was necrotic. Clear exudate was seen around the necrotic area. The entire left breast was immobile and attached to the chest wall. There was a single deep mass measuring 18 cm by 15 cm. The skin of the entire left breast had dark indurated papules that covered the entire left breast, crossed the midline and also invaded the skin of the right breast area.

The patient had constant severe pain of the left breast not relieved by pain medications. She had a consistently difficulty sleeping because of the pain, waking up several times each night. She was unable to wear a bra for several months prior to seeing me because any form of firm touch was very uncomfortable to her. Although she was sexually active prior to developing cancer, she had lost all desire for sexual activity since she was diagnosed. She also reported intermittent Pac's.

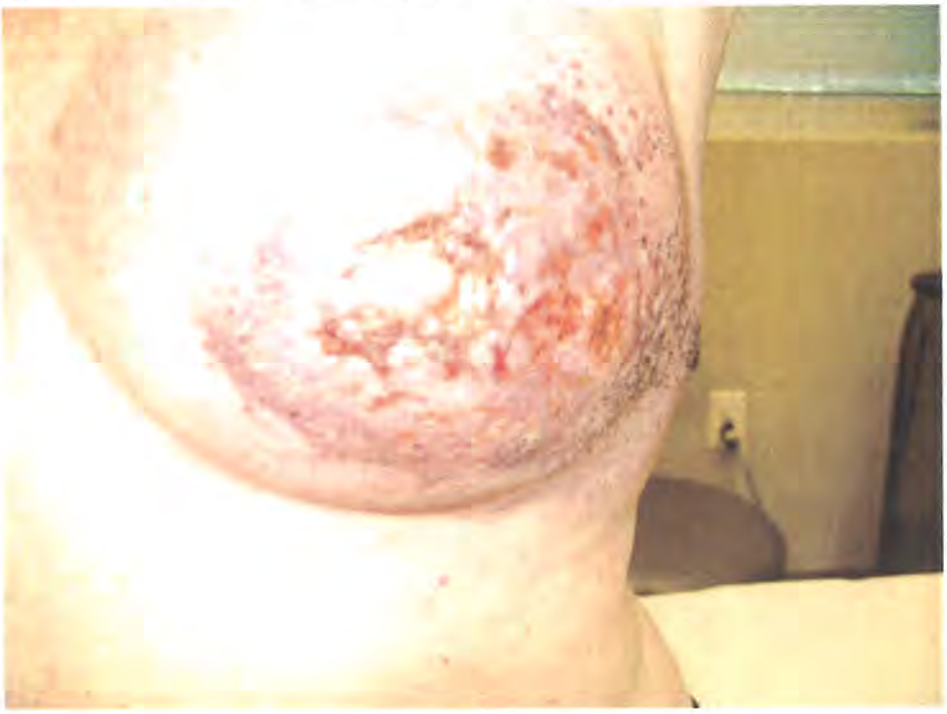


Image 1:

PRE-IECT TREATMENT:

OCTOBER 2008

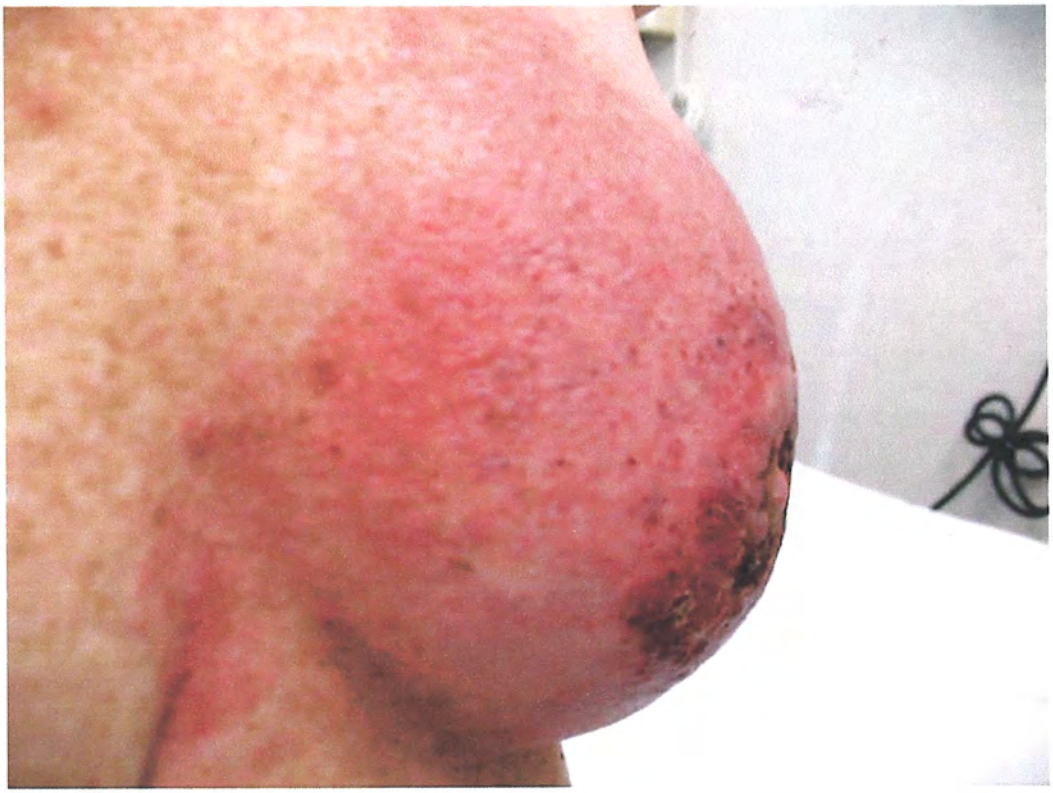


Image 2

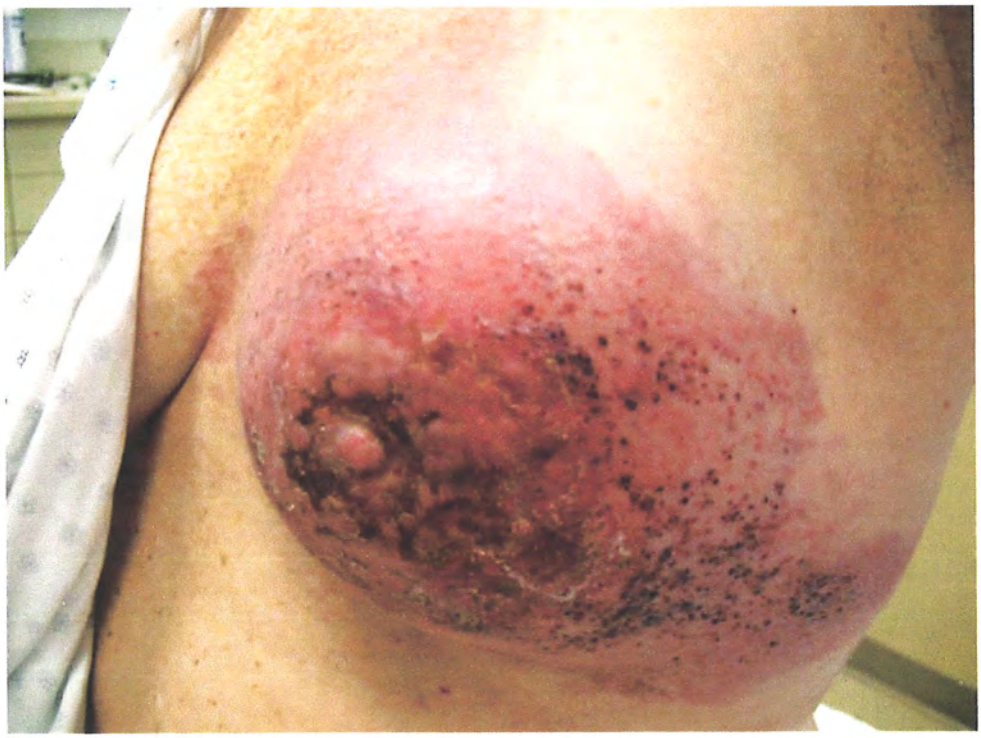


Image 3:
Images 1, 2 and 3 were taken before any treatment initiations

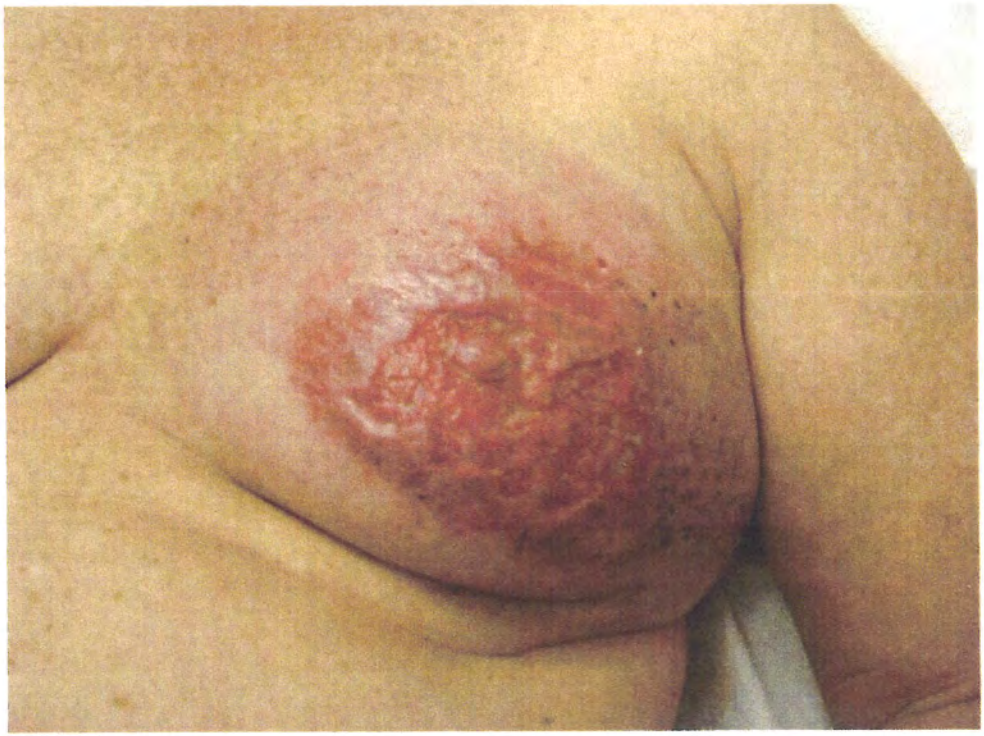


Image 4

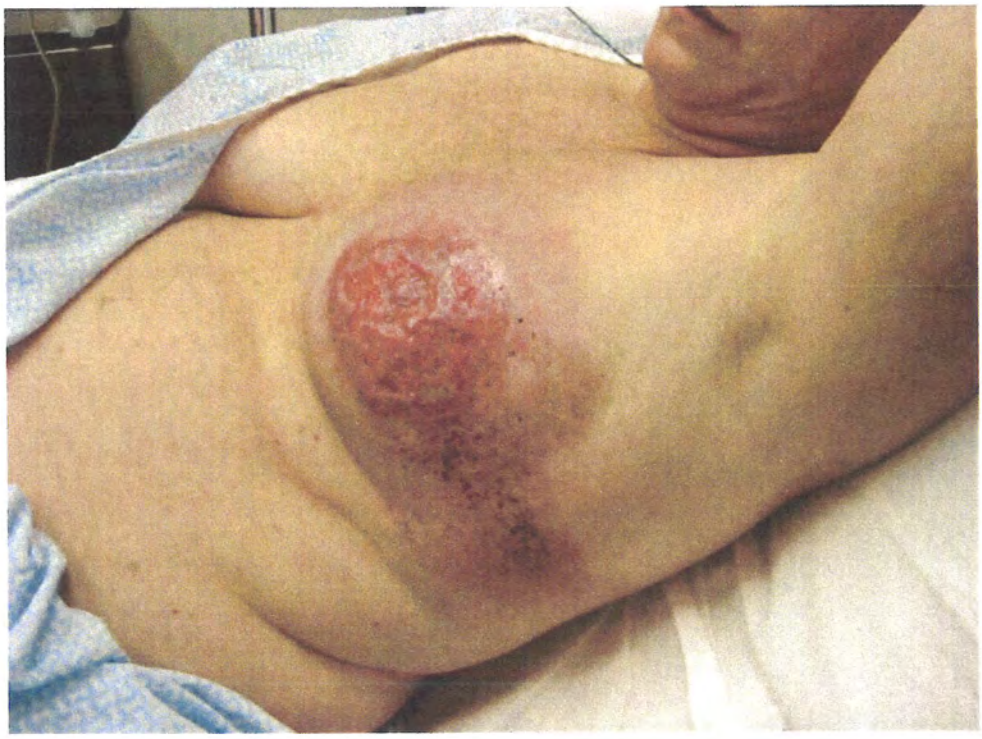


Image 4 & 5: These photos also precede Treatment #11 on 11/18/08. The papules are only seen on the lateral wall of the chest. They have decreased significantly in number.

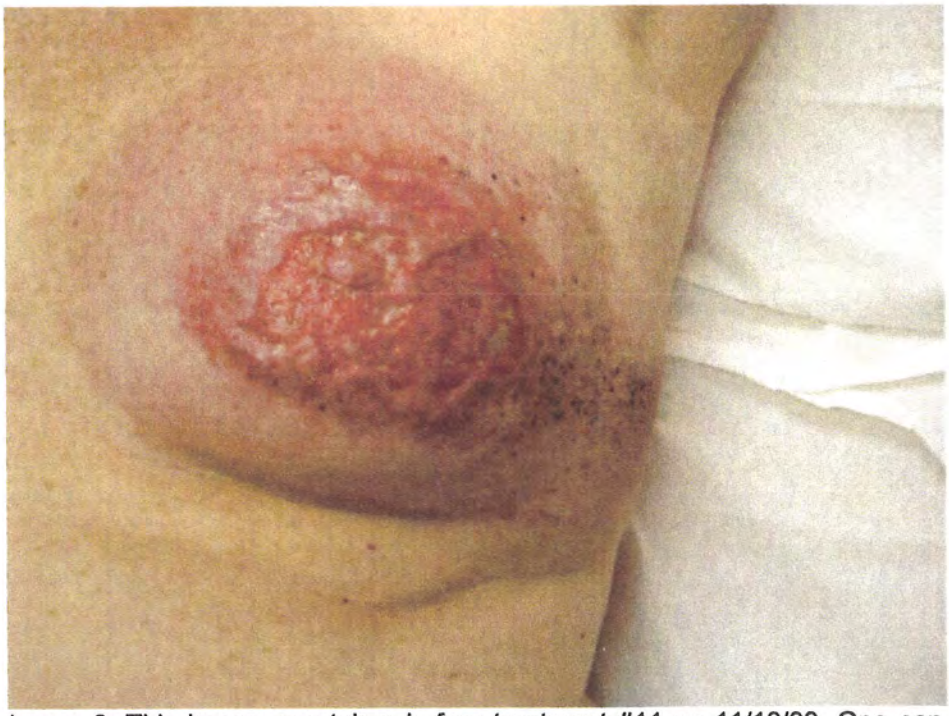


Image 6: This image was taken before treatment #11 on 11/18/08. One can see the necrotic tissue is gone. The nipple is visible and the skin is beginning to cover the previous necrotic area. The papules from the right breast and the medial part of the left breast are gone. The left breast is completely moveable away from the chest wall. There is no tenderness present at all on palpation or mobilization.

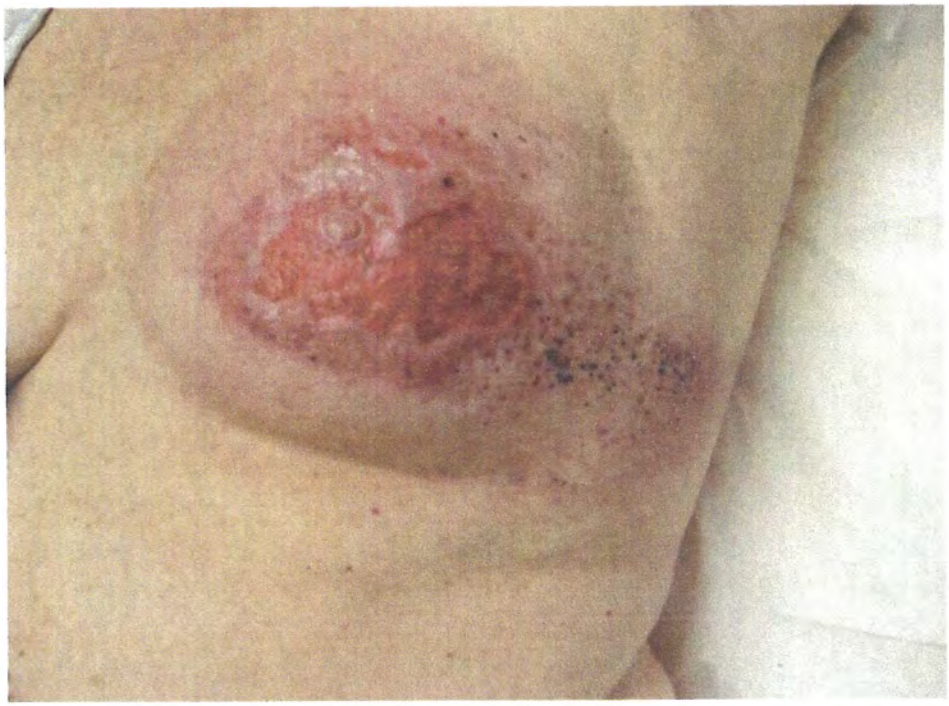


Image 7: This photo was taken on 11/25/08 before treatment #13. The ulceration is significantly reduced. The nipple is clearly visible. The skin is beginning to grow faster towards the nipple.

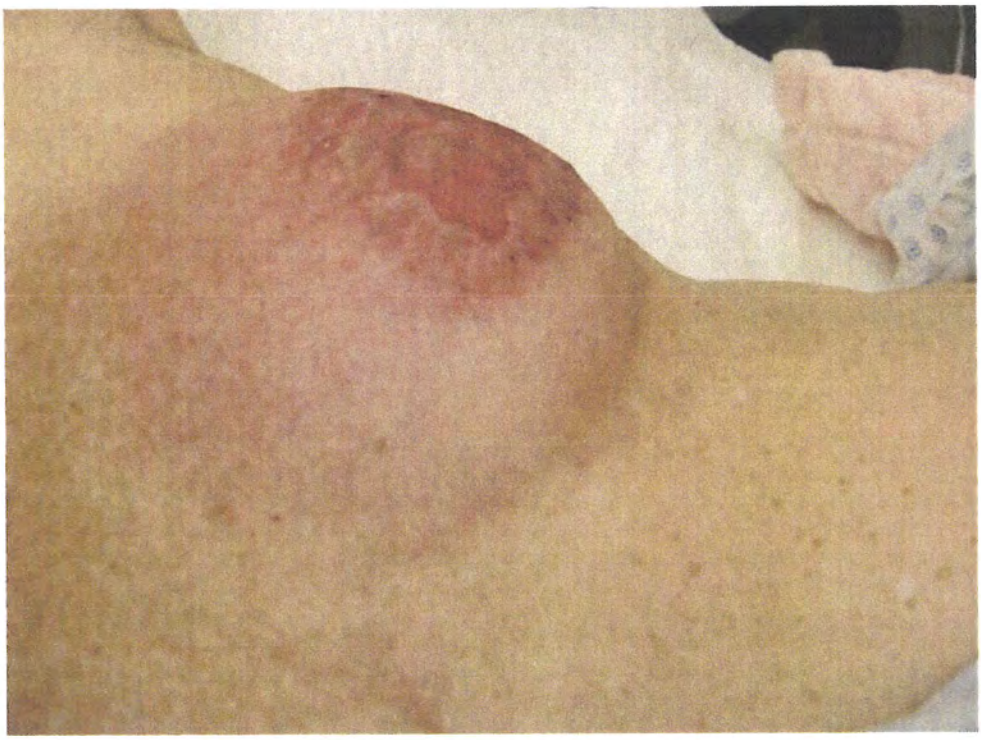


Image 8: This is a side view of 11/25/08 before treatment #13. The breast is clearly well defined and not attached to the wall. Re-epithelialization is towards normal is rapid.

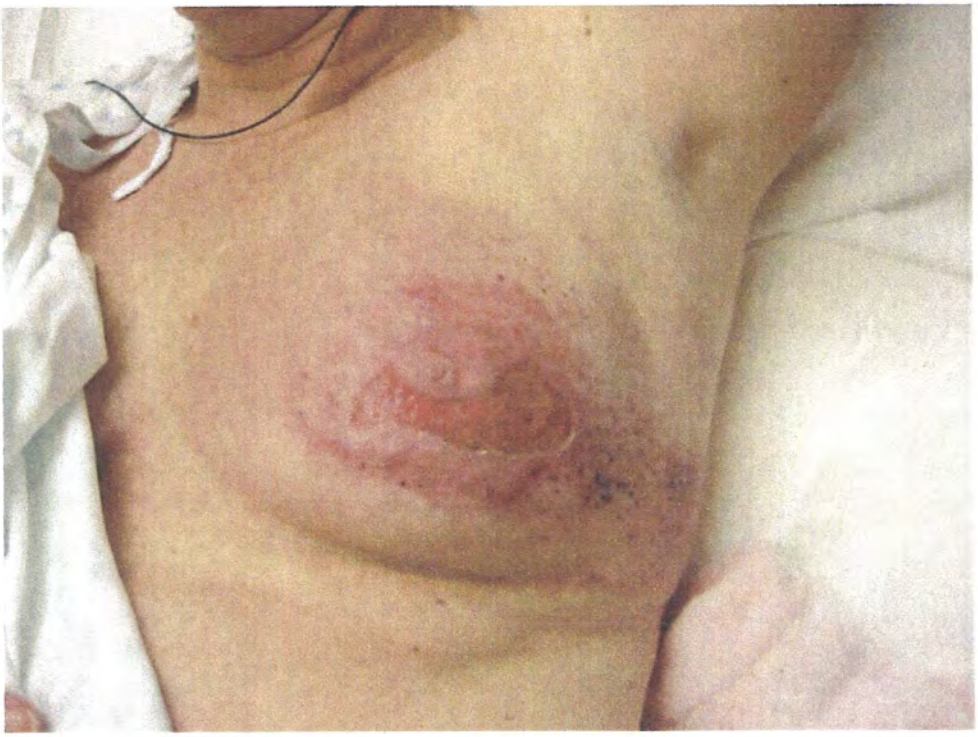


Image 9: Taken on 11/25/08 before treatment #13. This is a better resolution of the nipple which has clearly healed. Prior to any treatment only a few weeks ago, the nipple was almost indistinguishable.

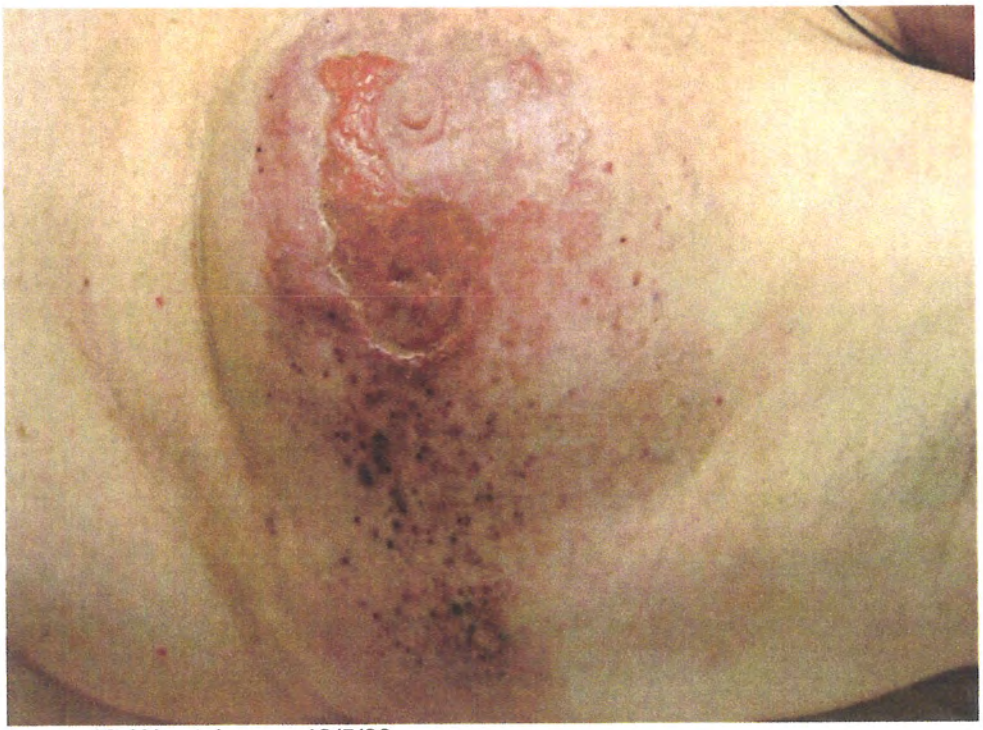


Image 10: Was taken on 12/5/08.

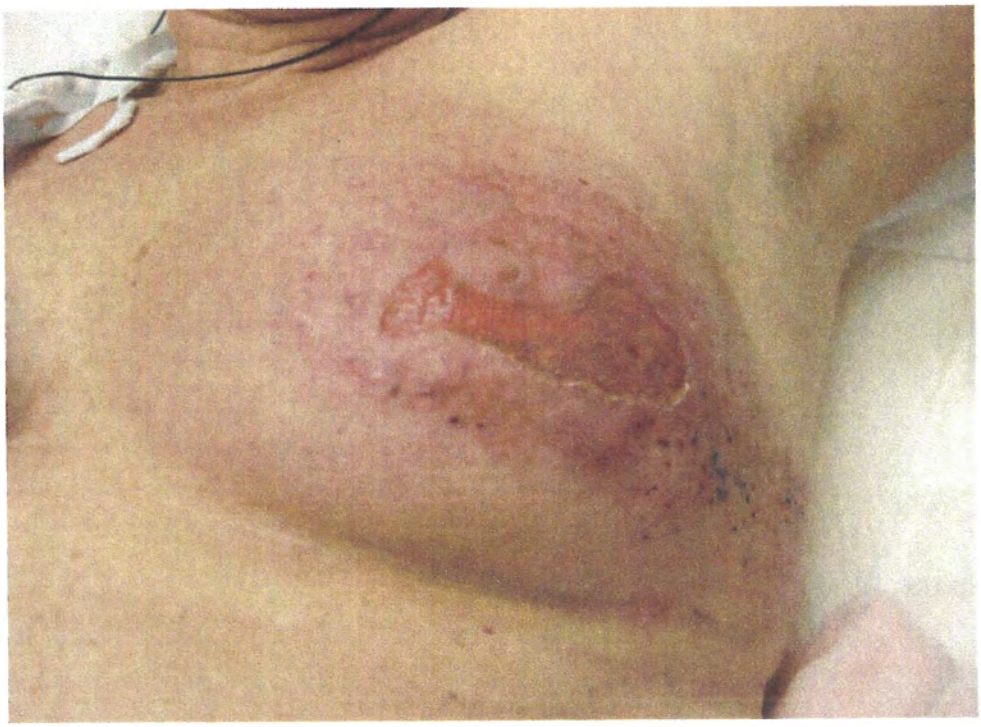


Image 11: Was taken on 12/5/08.

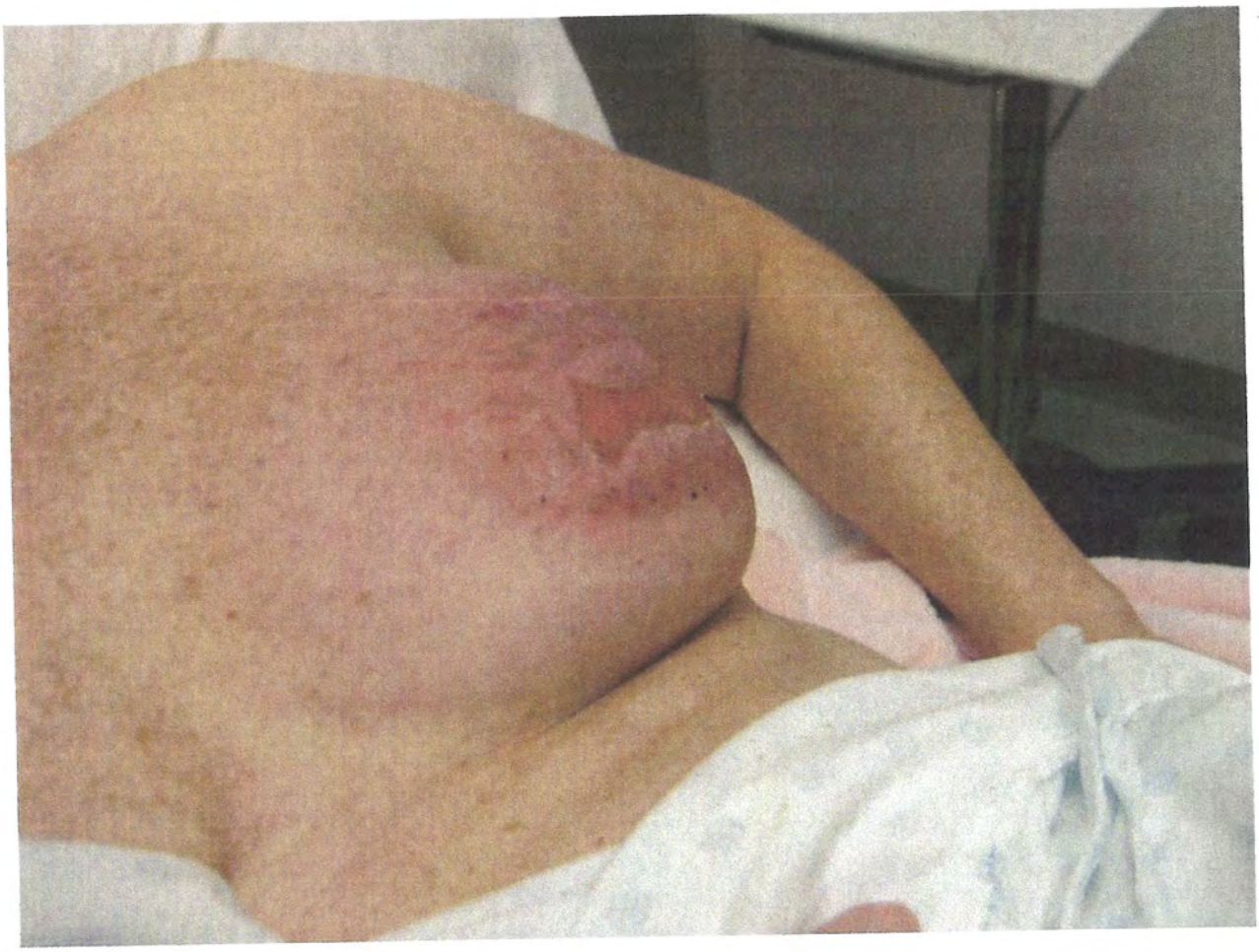


Image 12:
Images 10, 11 and 12 were taken on 12/5/2008, and healthy skin has almost covered all previous necrotic areas. The left breast has achieved normal size, shape and is completely mobile. Compared to the normal right breast, the only difference is the presence of the tumor mass and the incomplete re-epthelialization of the left breast.

MD IMAGING
1495 Gause Boulevard
Slidell, LA 70458
Phone: 985-405-5200
Fax: 985-405-5201

To:

Name: [redacted]
MRN #: 03-33-73 **Accession #:** 101006
Phone: [redacted] **DOB:** 05/02/1957
Exam Start: 10/13/08 4:12 pm **Gender:** Female
Referring Phys.:

Exam:
Clinical: STAGE 3B BREAST CANCER

WHOLE BODY FDG P.E.T./CT SCAN WITH IMAGE FUSION

CLINICAL INFORMATION: Staging of inflammatory breast cancer.

TECHNIQUE: Following I.V. administration of 14.4 mCi flourine-18 FDG, whole body P.E.T./CT images were obtained from the upper skull to the proximal thighs utilizing a dedicated GE full-ring PET/CT scanner with image fusion. There are no prior studies for comparison. The injection site was in the right antecubital fossa.

The patient's serum glucose level was 100 mg/dl.

FINDINGS: There is intense hypermetabolism in the left breast corresponding to multifocal large soft tissue masses seen on CT scan. Maximum SUV is 15.1. There is also prominent skin thickening of the left breast with maximum SUVs of 12.5 and this is compatible with a history of inflammatory breast cancer. There is multiple hypermetabolic metastatic left axillary lymphadenopathy. The larger axillary lymph nodes measure in the range of 2 cm in dimension with a maximum SUV of 8.2. There is a larger mass with less well defined margins and slight infiltration of the surrounding fat with the left axilla measuring 2.8 x 2 cm in dimension with a maximum SUV of 4.5, also likely related to a metastatic lymph node. Additional smaller lymph nodes are seen extending cephalad into the left superior subpectoral region, also compatible with metastasis. These lymph nodes are smaller with a maximum SUV ranging from 2.8 to 3.7. A tiny hypermetabolic focus in the left subclavicular region with a maximum SUV of 2.8 is suspicious for a subcentimeter metastatic lymph node. There is an elongated area of hypermetabolism seen in the mediastinum of the chest along the right paratracheal region, likely related to multiple small lymph nodes. Maximum SUV is 5.7. This extends to the level of the precarinal region. There is a 10 mm hypermetabolic lymph node in the right axilla with a maximum SUV of 3.3. Mildly hypermetabolic small lymph nodes are noted in the anterior mediastinum lateral aortic region with a maximum SUV of 3.2. A small hypermetabolic focus is seen anteriorly in the chest just laterally to the sternum on the left side suspicious for a small metastatic internal mammary lymph node. Very mild asymmetric prominence soft tissue prominence is seen on the CT scan. The maximum SUV is 3.4. CT scan demonstrates no pulmonary nodules. There is heterogeneous physiologic activity in the liver with no PET scan findings of hepatic or adrenal metastasis. A small hypermetabolic focus is seen in the posterior elements of the L3 vertebra on the right side and this is seen near the right L3-L4 facet joint, probably secondary to mild inflammatory change with no bony destructive lesions seen on the CT scan.

There is a hypermetabolic focus in the pelvis corresponding to a mass causing contour deformity of the posterior aspect of the body of the fundus of the uterus measuring up to 1.6 cm in dimension with a maximum SUV of 13.2. This is of undetermined etiology and further evaluation

[redacted] (Exam 101006) MRN #: 03-33-73

with ultrasound is recommended to exclude the possibility of uterine malignancy. A hypermetabolic focus in the left adnexa with a maximum SUV of 4.6 corresponding to a 14 mm focus of soft tissue attenuation on CT scan is also of uncertain etiology. Hypermetabolism may be seen within benign or malignancy ovarian masses and further assessment with a pelvic ultrasound is also recommended.

IMPRESSION: THERE IS A LARGE INTENSELY HYPERMETABOLIC MASS IN THE LEFT BREAST ASSOCIATED WITH SKIN THICKENING, COMPATIBLE WITH HISTORY OF INFLAMMATORY BREAST CANCER. THERE IS EVIDENCE OF METASTATIC DISEASE TO THE LEFT AXILLARY AND LEFT SUBPECTORAL LYMPH NODES, AS WELL AS PROBABLY METASTASIS TO A SMALL LEFT SUPRACLAVICULAR LYMPH NODE. THERE IS ALSO EVIDENCE OF METASTATIC DISEASE TO THE MEDIASTINAL LYMPH NODES IN THE CHEST WITH PROBABLY METASTATIC LYMPH NODES TO THE RIGHT AXILLA AND LEFT INTERNAL MAMMARY CHAIN.

A SMALL HYPERMETABOLIC FOCUS AT THE LEVEL OF THE L3 VERTEBRA IS PROBABLY A BENIGN ETIOLOGY.

HYPERMETABOLISM IN THE PELVIS INVOLVING THE POSTERIOR UTERUS AND LEFT ADNEXA IS POTENTIALLY OF BENIGN ETIOLOGY; HOWEVER, CORRELATION WITH CLINICAL FINDINGS AND PELVIC ULTRASOUND IS RECOMMENDED.

Interpreting Radiologist

Kelvin McDaniel MD

KELVIN P. MCDANIEL, MD

Electronically Signed: 10/15/08 8:24 am

Thank you for referring [redacted] to MD IMAGING.

Printed: 4/22/2009 2:28 pm [redacted] (Exam 101006) Page 2 of 2

MD IMAGING
1495 Gause Boulevard
Slidell, LA 70458
Phone: 985-405-5200
Fax: 985-405-5201

To:

Name: [redacted]
MRN #: 03-33-73 **Accession #:** 106804
Phone: [redacted] **DOB:** 05/02/1957
Exam Start: 12/10/08 1:31 pm **Gender:** Female
Referring Phys.:

Exam:
Clinical: BREAST CA

WHOLE BODY FDG P.E.T./CT SCAN WITH IMAGE FUSION

CLINICAL INFORMATION: Restaging of breast carcinoma.

TECHNIQUE: Following I.V. injection of 15.35 mCi flourine-18 FDG, into the right antecubital vein, total body P.E.T./CT were performed from the mid face to the upper thighs utilizing a dedicated full-ring GE scanner.

The patient's serum glucose level was 101 mg/dl.

FINDINGS: There is a marked favorable change, with marked decrease in the masses seen in the left breast and there is also mild decreased hypermetabolism within the residual breast mass. The maximum SUV within the breast mass is 2.4 and in the overlying skin it is 7.4. The residual hypermetabolism could very well also be due to radiation therapy/chemotherapy.

There is complete regression of the enlarged left axillary lymph nodes. There is no abnormal hypermetabolism in the axillary or the mediastinal lymph nodes that was seen and described previously.

There are no new foci of abnormal hypermetabolism in the neck, chest, abdomen, pelvis or the skeletal system.

On the CT scan, the lungs are clear. The CT shows mild decrease in the bulk of the tumor in the left breast.

The CT scan shows no other significant findings.

IMPRESSION: THERE HAS BEEN A MARKED FAVORABLE CHANGE AS DETAILED ABOVE, WITH MILD REDUCTION OF THE MASS IN THE LEFT BREAST AND NO LONGER EVIDENCE OF ABNORMAL UPTAKE IN THE LYMPH NODES THAT WAS SEEN PREVIOUSLY.

Interpreting Radiologist
KISHORE V. KAMATH, MD

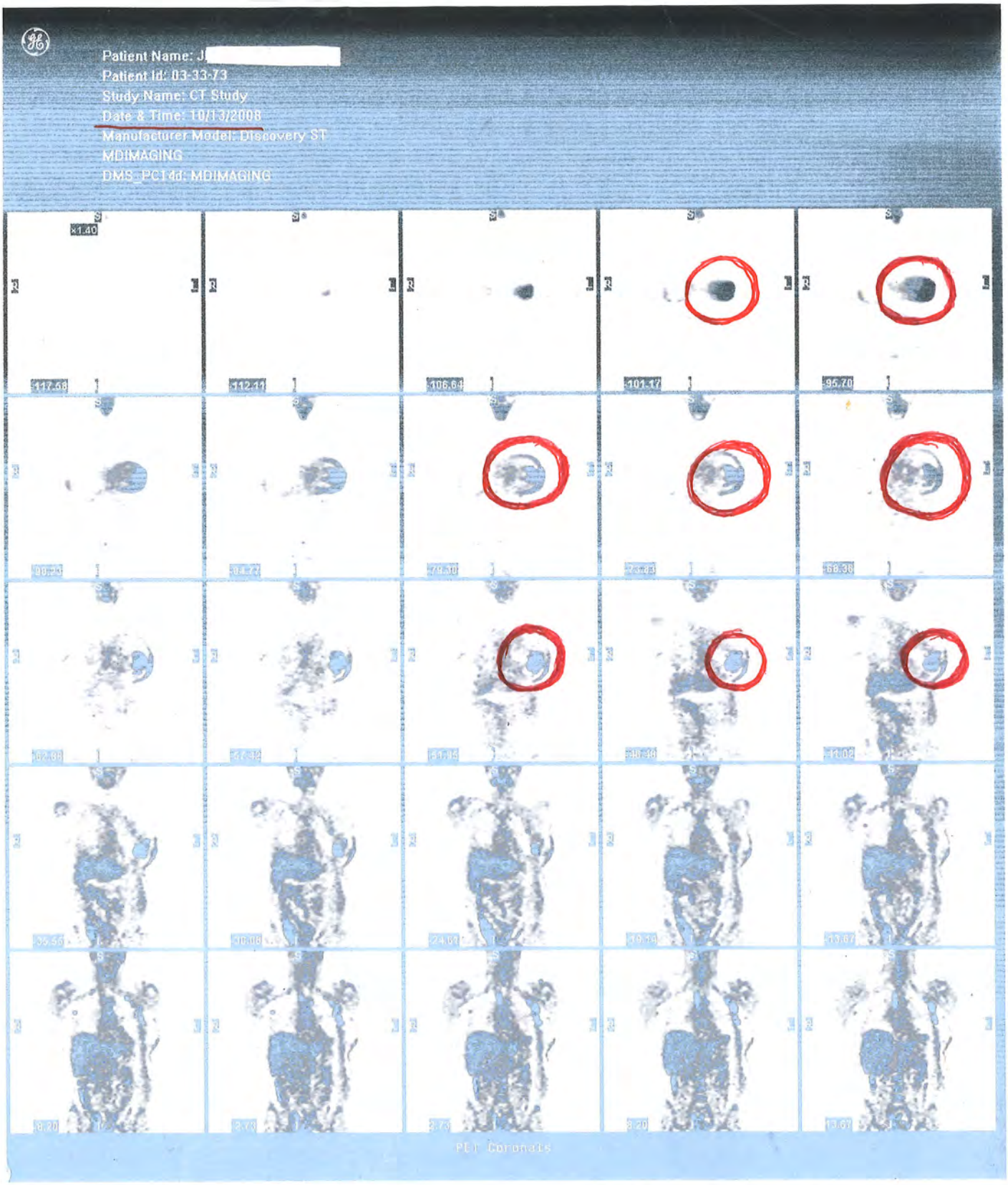
Proxy Radiologist
RICHELLE C. LEGNON, MD

Dictated: 12/10/08 3:58 pm

Electronically Signed: 12/11/08 11:14 am

PRE-IECT TREATMENT:

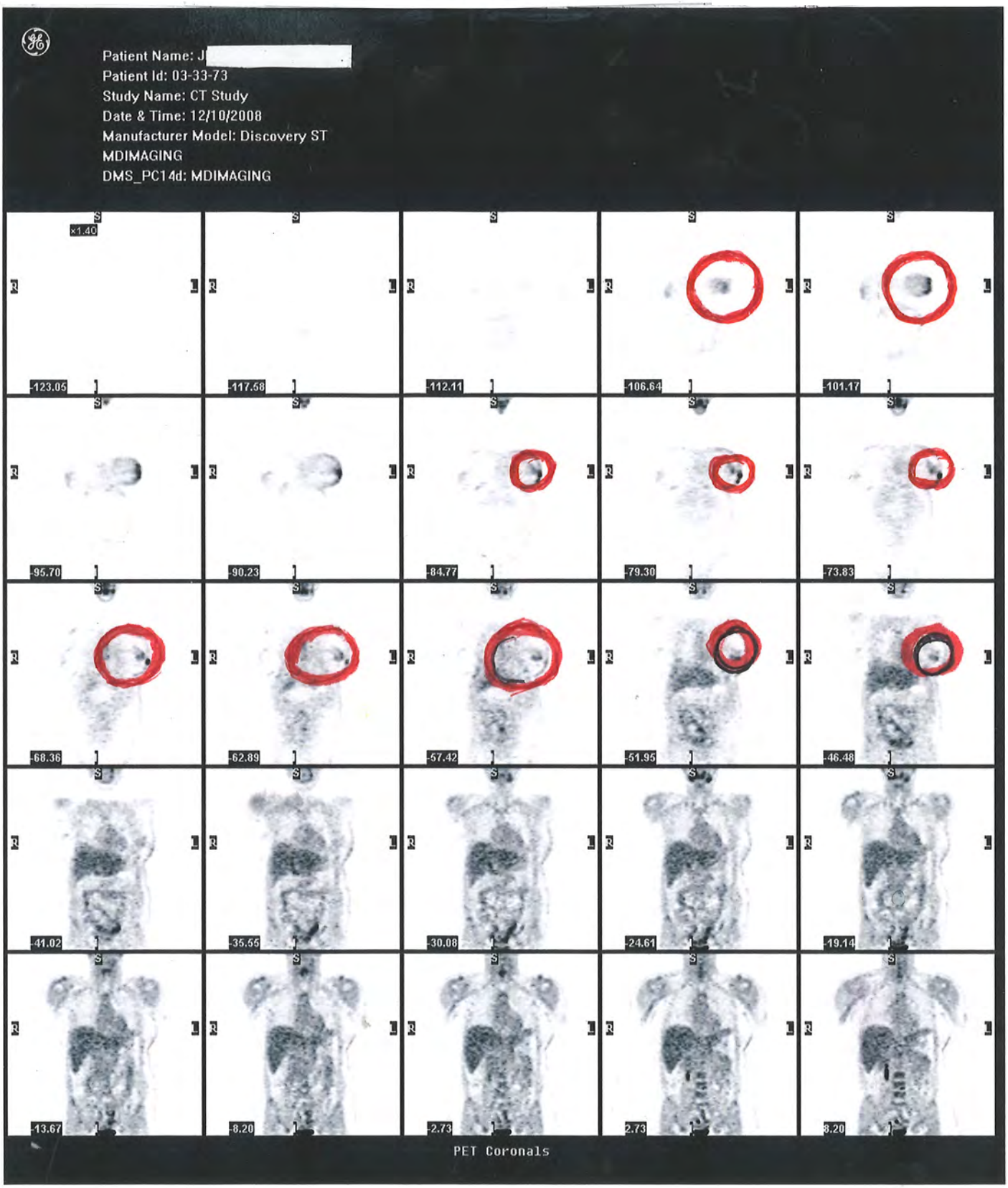
OCTOBER 2008



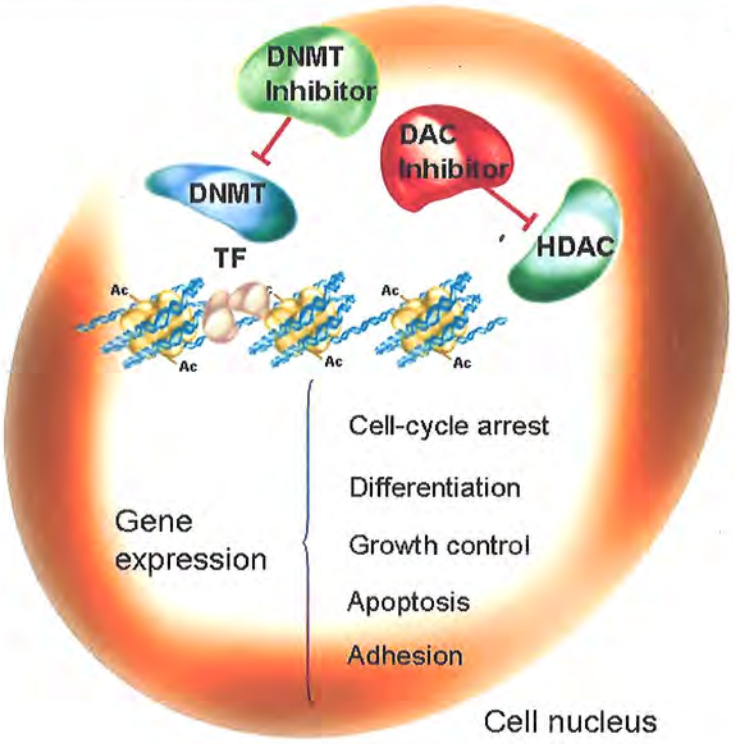
Interpreting Radiologist	**Kelvin McDanuiel MD**
Interpreting Radiologist	**Kishore V. Kamath MD**
Proxy Radiologist	**Richelle C Lignon MD**

POST-IECT TREATMENT:

DECEMBER 2008



Therapeutic Targeting of Both Histone and DNA Modifications Can Synergize



- Since DNA methylation and histone deacetylation can co-operate to silence tumor suppressors, inhibition of both DNMT and HDAC activities can synergize to restore expression of silenced genes

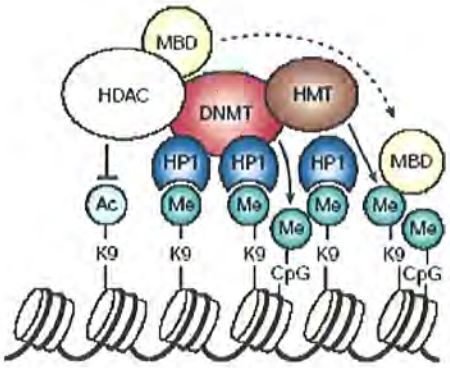
IntraTherapies

Clinical Protocol IECT Trivalent Compound

Developer **Nathan Sassover**

Application No.: Not Yet Assigned
Docket No.: 674443000100
Inventor: Nathan SASSOVER
Title: EPIGENETIC THERAPEUTICS IN THE TREATMENT OF CANCER

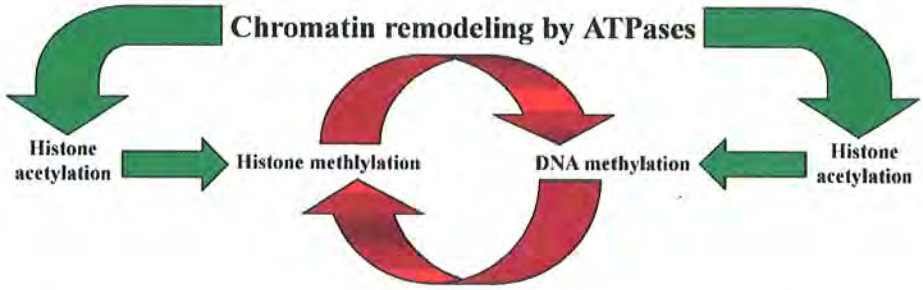
The DNA Methylation Machinery Interacts with the Histone Modification Machinery



DNMTs interacts with:

- **Histone deacetylases (HDACs)**
- **Histone methylases (HMTases)**
- **ATP-dependent chromatin remodelers**
- **Chromatin structural proteins (HP1 family)**

Cooperative and self-reinforcing organization of the chromatin & DNA-modifying machinery responsible for gene silencing in normal & malignant cells

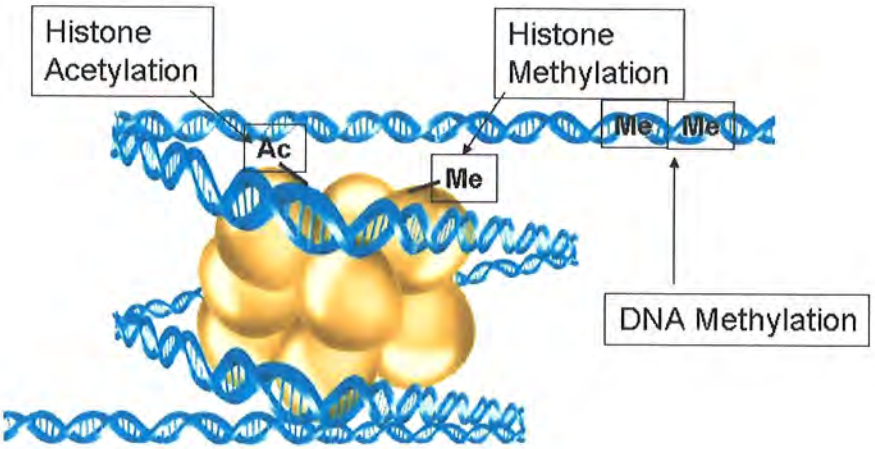


What comes first, histone deacetylation, histone methylation, or DNA methylation?

Application No.: Not Yet Assigned
Docket No.: 674443000100
Inventor: Nathan SASSOVER
Title: EPIGENETIC THERAPEUTICS IN THE TREATMENT OF CANCER

Basic Epigenetic Mechanisms: Post Translational Modifications to Histones and Base Changes in DNA

- Epigenetic modifications of histones and DNA include:
  - Histone acetylation and methylation, and DNA methylation

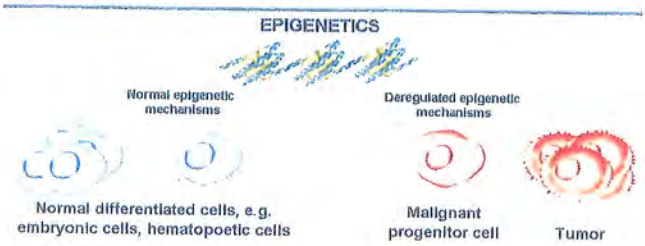


IntraTherapies

Application No.: Not Yet Assigned
Docket No.: 674443000100
Inventor: Nathan SASSOVER
Title: EPIGENETIC THERAPEUTICS IN THE TREATMENT OF CANCER

A

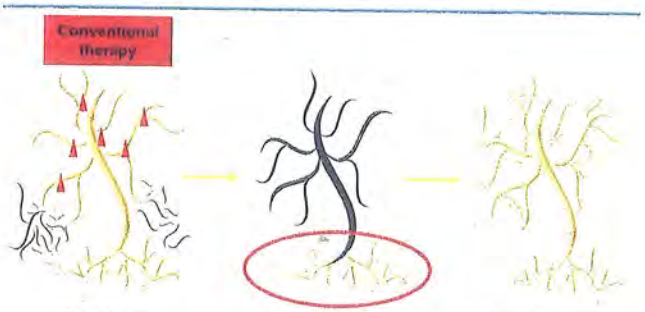
Epigenetics Play Important Roles in Normal Cellular Development and in Cancer



- Epigenetic mechanisms can regulate genes involved in differentiation, cell cycle, and cell survival
- Deregulation of epigenetic mechanisms results in aberrant gene expression, which can lead to cancer
- Reversal of deregulated epigenetic changes is a rational strategy for targeting cancer

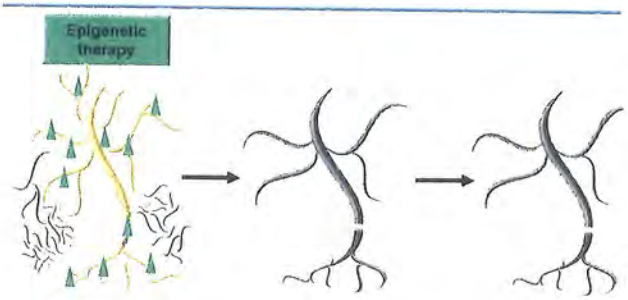
B

Conventional Therapies May Target Tumor Cells, Not Cancer Stem Cells



C

Epigenetic Therapy May Target Cancer Stem Cells and Tumor Cells



Application No.:
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