

Editorial

Targeted therapy is the result of 100 years of research dedicated to understanding the difference between cancer cells and normal cells. Toxic chemotherapeutic agents are slowly being supplemented by a new generation of drugs that recognize specific targets in or on cancer cells. The Special Feature in this issue of the **Cancer News** highlights Targeted Therapy in Cancer.

The 21st century approach to medicine is progressively adopting molecular methods to diagnosing and treating disease. Molecular imaging allows clinicians to visualize the expression and activity of specific molecules and biological processes that influence tumor behavior and/or response to therapy. "Perspective" gives an overview of Molecular Imaging in Cancer.

"In Focus" highlights Merck Serono's Erbitux® (Cetuximab), a novel therapy and an important step forward in the battle against colorectal cancer. It is also approved for the treatment of locally advanced squamous cell carcinoma of head & neck in combination with radiotherapy. The feature "Institute" profiles the Christus Stehlin Foundation, USA, which has pioneered some notable firsts and established their reputation internationally as a premier cancer research and treatment facility.

"Research & Development" and "New Technologies" cover in nutshell information on recent advances in research that could be of interest to scientists and medical professionals. The feature on "Watch-Out" covers new patents published worldwide. "Globe Scan" gives a glimpse of some of the recent inventions published around the globe.

Merck Serono is the new division for innovative small molecules and biopharmaceuticals of Merck. Headquartered in Geneva, Switzerland, Merck Serono discovers, develops, produces and commercializes innovative products to help patients with diseases with unmet needs. A special thanks to Merck Serono Oncology for funding this issue of Cancer News.

"Activities of the Institute" includes a presentation on Tomotherapy and IGRT by Tomotherapy Inc., USA on October 1; Home Cancer Care Meet, a get-together organized by RGC&RC on October 6 for the families of cancer patients; CME on Chronic Myeloid Leukemia; and announcement about the 7th Annual International Conference, RGCON 2008, having its main theme as "Colorectal Cancer" that Rajiv Gandhi Cancer Institute and Research Centre is holding on March 8 - 9, 2008 in Delhi.

The Institute gratefully acknowledges the contributions made by Dr JB Sharma, Dr DC Doval, Dr (Col.) R Ranga Rao, Dr PS Choudhury, Dr AK Anand, Prof P S Negi, Dr Sunil Khetrapal, Dr Dinesh Bhurani, Dr Monica Malik and Ms Anita Kumari. Wishing our readers a happy, prosperous and healthy New Year 2008.

Dr (Mrs) Ira Ray
Director Research

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This publication aims at disseminating information on pertinent developments in its specific field of coverage. The information published does not, therefore, imply endorsement of any product/process/ producer or technology by **RGC&RC**.

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Printed and Published by
Rajiv Gandhi Cancer Institute and
Research Centre, Sector - V
Rohini
Delhi - 110085

Printed at Sagar Printers,
1880 Udaichand Marg,
Kotla Mubarakpur
New Delhi - 110003.

SPECIAL FEATURE

TARGETED THERAPY IN CANCER

Introduction

Cancer therapy is getting smarter with new generation of targeted cancer therapies that recognize specific targets in or on cancer cells that block the growth and spread of cancer. Targeted cancer therapies affect proteins and signaling pathways, unique to the malignant cells and leave the normal cells alone. These therapies may be more effective than the current treatments and less harmful to the normal cells. Conventional cancer treatments, such as chemotherapy and radiation therapy, cannot distinguish between cancer cells and healthy cells. Consequently, healthy cells are commonly damaged in the process of treating cancer, which results in side effects which may be severe, reducing a patient's quality of life. Likewise, surgery can cause "tremendous collateral damage" although recent technological advances have dramatically improved.

There are about 30 different "targeted therapies" that have been approved by the US Food and Drug Administration (FDA) or are still in development. These therapies are being studied for use alone, in combination with each other and in combination with other cancer treatments, such as chemotherapy. Today, some of the new targeted therapies are "nearly miraculously effective".

Types of Targeted Therapies

1. Monoclonal Antibodies

They attach to tumor cells and either mark the cells for attack by the immune system, block specific transmembrane receptors or deliver chemotherapeutic or radioactive drugs.

Some surface antigens are present predominantly or exclusively on malignant cells and not the surrounding normal cells. These tumor associated antigens make excellent targets for specific antibodies to bind to. When some of these antibodies bind to the tumor cells, they can trigger a host of immune reactions that lead to cell death.

This technology allows treatment to target specific cells, causing less toxicity to the healthy cells. Monoclonal antibody therapy can be done only for cancers in which antigens have been identified. They may be used in cancer treatment in a number of ways:

- a) MOABs that react with specific types of cancer may enhance a patient's immune response to the cancer.
- b) MOABs can be programmed to act against the cell growth factors, thus interfering with the growth of cancer cells.
- c) MOABs may be linked to anticancer drugs, radioisotopes (radioactive substances), other biological response modifiers or other toxins. When the antibodies latch onto the cancer cells, they deliver these poisons directly to the tumor, helping to destroy it. MOABs carrying radioisotopes may also prove useful in diagnosing certain cancers, such as colorectal, ovarian and prostate etc.

FDA approved monoclonal antibodies for the parenteral use in the detection and treatment of cancer with the mechanism of action and cancer indications are given in Table 1.

2. Agents that Control Proliferation

These drugs inhibit signally pathways for growth and proliferation within the tumor cells.

Malignant cells can proliferate indefinitely and loose the normal signals that tell them to undergo apoptosis. Normal cell growth and replication is a very complicated and organized process. DNA contains the code for the synthesis of various proteins, including growth factors that bind to the surface receptors of the same cell or cells of the surrounding or distant tissues. This binding activates the signaling pathways within the cell that relay information back to the nucleus and activate mechanisms responsible for cell division and proliferation. Abnormalities along these pathways can lead to malignant transformation and uncontrolled cell proliferation. These abnormalities can be targeted to inhibit cell proliferation, induce apoptosis, or both.

Surface Receptors - Most surface receptors that are aberrant in malignancies are enzyme-linked. There are four classes of enzyme-linked receptors: guanylyl cyclases, tyrosine phosphatases, serine/threonine kinases and protein-tyrosine kinases. The latter three play an important role in malignant transformation.

Protein - Tyrosine Kinases - Protein-tyrosine kinases are transmembrane or cytosolic enzymes that transfer a phosphate group from adenosine triphosphate to a specific amino acid in the proteins after a factor, such as epidermal growth factor binds to its receptor. This leads to the

activation of signaling pathways. Included in this process are many growth factors, differentiation factors and hormones, many of which have been implicated in cell growth, differentiation, proliferation and death which may be involved in tumor progression and metastasis.

So far, more than 100 protein-tyrosine kinases have been identified, including epidermal growth factor receptor, platelet derived growth factor receptor, vascular endothelial growth factor receptor and cytosolic Abelson (Abl) tyrosine kinase.

Epidermal Growth Factor Receptors - Epidermal growth factor receptors have an established role in carcinogenesis and tumor growth and they are prime targets for therapy. There are four types of epidermal growth factor receptors: Erb B-1 (HER 1), Erb B-2 (HER 2, HER 2/neu), Erb B-3 (HER 3) and Erb B-4 (HER 4). These receptors bind a wide variety of ligands and are present on many solid epithelial tumors, including cancers of the head and neck, lung, colon, breast and kidney. Their expression may be associated with early metastasis and poor outcome.

Blocking Protein-Tyrosine Kinases - Drugs that inhibit cell surface receptors have shown promising clinical results. Two types of agents are used to block or inhibit the protein-tyrosine kinases:

- Monoclonal antibodies, which inhibit the extracellular part of the receptor.
- Small molecular drugs which inhibit the intracellular portion.

Some of the protein-tyrosine kinase inhibitors approved are trastuzumab, imatinib, gefitinib, sunitinib, sorafenib etc.

- i) Trastuzumab (Herceptin) inhibits cell growth by binding the extracellular part of the HER2 protein, which is involved in the pathogenesis of breast and ovarian cancer.
- ii) Imatinib (Gleevec) is an inhibitor of Bcr-Abl and c-kit tyrosine kinases. It has been approved for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors. Toxic effects are nausea, diarrhea, myalgia and edema.
- iii) Gefitinib (Iressa) has been approved for third-line treatment of non-small cell lung cancer. Toxic effects are diarrhea, nausea, rash and pulmonary toxicity.
- iv) Sunitinib (Sutent) is a multi kinase inhibitor and is indicated for first line metastatic renal cell carcinoma.
- v) Sorafenib (Naxavaar) is also a multi kinase inhibitor and has demonstrated efficacy as first line metastatic renal cell carcinoma.

Table: 1 FDA Approved Monoclonal Antibodies

Generic Name	Trade Name	Agent/Target	Cancer Indication
Unconjugated			
Rituximab	Mabthera	Chimeric anti-CD20 IgG ₁	B-cell lymphoma
Trastuzumab	Herceptin	Humanized anti-HER2 IgG ₁	Breast
Alemtuzumab	Campath-1H	Humanized anti-CD52	Chronic lymphocytic leukemia
Cetuximab	Erbitux	Chimeric anti-EGFR	Colorectal, Head & Neck
Bevacizumab	Avastin	Chimeric anti-VEGF	Colorectal
Radio conjugates			
Satumomab pendetide	OncoScint	¹¹¹ In-murine anti-TAG-72 IgG	Colorectal, ovarian
Nofetumomab Merpentan	Verluma	^{99m} Tc-murine anti-EGP-1 Fab	Small cell lung carcinoma
Arcitumomab	CEA-Scan	^{99m} Tc-murine anti-CEA Fab	Colorectal
Capromab pendetide	Prosta Scint	¹¹¹ In-murine anti-PSMA	Prostate
Ibritumomab tiuxetan	Zevalin	⁹⁰ Y-murine anti-CD20 IgG	B-cell lymphoma
Tositumomab	Bexxar	¹³¹ I-murine anti-CD20 IgG + unlabeled tositumomab	B-cell lymphoma
Drug conjugates			
Gemtuzumab ozogamicin	Mylotarg	Humanized anti-CD33 IgG ₄ conjugated to colicheamicin	Acute myelogenous leukemia

Blocking Intracellular Signaling Pathways - Signaling pathways within malignant cells can also be inhibited. One enzyme that has been targeted is farnesyl transferase which activates the Ras protein, a proto-oncogene involved in growth factor signaling. Ras is overexpressed in a variety of solid tumors and hematologic malignancies. Small molecules that inhibit farnesyl transferase appear to have an activity in various malignancies and have acceptable toxicities. These drugs remain experimental.

Proteasome Inhibitors - A recently explored target present in all cells is a multi-enzyme complex called proteasome. The function of proteasome that is exploited in experimental therapy is degradation of proteins that regulate cell cycle progression. Proteasome inhibition is a novel approach to the treatment of solid tumors. PS-347 (bortezomib) is a small cell permeable molecule that has been established as an important target in hematologic malignancies and has demonstrated efficacy for the treatment of patients with recurrent and refractory multiple myeloma. It induces apoptosis of malignant cells through the inhibition of NF- κ B and stabilisation of proapoptotic proteins.

Angiogenesis Inhibitors - Angiogenesis means the formation of new blood vessels. It plays an important role in the growth and spread of healthy and cancerous tissue and its inhibitors starve the cancer cells of the blood that they need to survive and grow. Currently, there are more than 20 compounds being tested on a variety of cancers in clinical trials. Some of these angiogenesis inhibitors are available commercially, approved by the FDA for other uses e.g. Bevacizumab as first-line treatment for metastatic colorectal cancer with chemotherapy (FOLFOX regimen).

3. Gene Therapy

This kind of therapy holds great promise for blocking expression of oncogenes or replacing missing or defective tumor suppressor genes. Many genes have oncogenic potential; these are categorized as either tumor-suppressor genes or oncogenes.

Replacing Defective or Absent Tumor-Suppressor Genes: Tumor-suppressor genes normally keep cell replication in control, and if they are absent or their function is decreased, cell can turn malignant. An example is the p53 gene, which is mutated in many malignancies or absent in certain inherited cancers. Mutant or missing tumor-suppressor genes can be replaced in vivo.

Blocking Oncogenes: Oncogenes can induce malignant transformation if their functioning is increased. Mutated or overexpressed oncogenes can be inactivated or down-regulated using antisense oligonucleotides or ribozymes.

- Antisense oligonucleotides are short pieces of synthetic DNA or RNA. They can block gene expression by binding to their complementary strands of DNA or RNA. The most common target is messenger RNA (mRNA). Binding to mRNA cleaves it and inhibits the synthesis of protein in question.
- Ribozymes are enzymes that catalyze the cleavage of RNA. They can be used therapeutically to cleave RNAs, such as Bcr-Abl transcript involved in chronic myelogenous leukemia. A major obstacle remains the lack of efficient and selective vectors to deliver genes.

Molecular Signatures

It's clear that the more specific a target therapy is in terms of its target, the more restricted the patient population would be that benefits from that drug. If researchers could find what subpopulations of tumors are driven by particular pathways, they could then find drugs to target those pathways which would be very effective in that subpopulation. Researchers are searching molecular signatures or "profiles" which would be the key to successfully using targeted therapies and moving them to earlier stages of treatment.

Impact on Cancer Treatment

Targeted cancer therapies will give doctors a better way to tailor cancer treatment. Eventually, treatment may be individualized, based on the unique set of molecular targets produced by the patient's tumor. Targeted cancer therapies also hold the promise of being more selective, thus harming fewer normal cells, reducing side effects and improving the quality of life. Some of the targeted cancer therapies are envisioned as the magic bullets of cancer treatment. Traditional chemotherapy and radiation therapy won't disappear anytime soon, but more and more they will be supplemented by therapies that target tumor cells without affecting the normal cells.

(The Institute appreciates Dr J B Sharma, Dr D C Doval and Dr (Col) R Ranga Rao for their contribution to this Special Feature on Targeted Therapy in Cancer).

PERSPECTIVE

MOLECULAR IMAGING IN CANCER

Introduction

Molecular Imaging (MI) is an emerging field that aims to integrate patient and disease-specific molecular information and conventional imaging. It provides noninvasive or minimally invasive techniques to diagnose, characterize or monitor tumors before and after a therapeutic intervention. It can also be used to study tumor gene expression, optimize planning and new drug developments.

Molecular Imaging Techniques

(i) *Nuclear Imaging*: Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) have the advantage of high intrinsic sensitivity and depth penetration. Both are quantitative but have limited spatial resolution. Introduction of PET-CT/SPECT-CT integrated system has overcome this limitation and is playing an ever increasing role in clinical molecular imaging. One commercial cyclotron is able to cater to many institutions making this a cost effective and clinically viable option today.

(ii) *Magnetic Resonance Imaging (MRI) and Ultrasound*: These offer high spatial resolution (<1mm). MRI provides soft tissue and functional information through proton density perfusion, diffusion and biochemical contrasts allowing co-registration of molecular and anatomical information: microbubbles, liposomes or perfluorocarbon emulsions as scaffolds have been used as targeted agents for ultrasound.

(iii) *Optical Imaging*: It is an emerging modality and involves detection of photons after their interaction with tissue and in particular, near infrared fluorescence (NIRF) imaging. The advantages of fluorescence imaging methods include improved relative sensitivity, high resolution and the availability of a variety of imaging reporters and signal amplification strategies. It is a convenient way to co-register surface anatomical information with molecular information and has been applied to retinal angiography, cardiovascular surgery, and gastrointestinal endoscopy using either indocyanine green enhancement or autofluorescence. Surface weighted nature, effects of blood absorption and autofluorescence are its limitations.

Targets and Agents

It defines the disease at a molecular level much

earlier than a structural change. Development of in-vivo agents are challenging, although many in-vitro agents have been developed.

Tumor Molecular Process

These techniques probe the following tumor molecular processes: metabolic imaging glucose and amino acid metabolism, cell proliferation imaging, oxygenation imaging, somatostatin receptors, estrogen receptors, angiogenesis imaging, apoptosis imaging, gene expression and cell tracking. The measurement of these parameters can be used to give an early indication of the response to treatment, drug resistance and/or recurrence.

Applications in Cancer

- i) Cancer detection by nuclear molecular agents have been described for the detection of occult cancers. Optical imaging, using novel NIRF MI probes, is used with tomographic techniques or high spatial resolution endoscopic imaging. This has been used for breast cancer, muscle and brain imaging.
- ii) PET-CT, MI agents and nanoparticle enhanced MRI can have an impact on the staging of various cancers, upstaging or even down staging a particular disease. However, what impact these have on the management and outcome, needs to be seen.
- iii) Drug Development & Therapy Assessment markers can be used as end points for monitoring therapy or as representing a molecular target for assessing the efficacy and biodistribution. Imatinib response to gastric stromal tumors is one such example.
- iv) Biomedical research improves the understanding of the disease and can enhance the efficacy of oncologic research.

Future Perspective

Molecular imaging would increasingly become a part of personalized treatment planning and pharmacogenomics by complementing the existing methods to diagnose microscopic and subclinical disease, provide a molecular basis for tailored disease therapy and assess the efficacy of molecular therapeutics. There is a need to validate and standardize the international clinical MI protocols for diagnosing disease, guiding therapy, detecting recurrences and drug resistance. MI would be the future of oncologic research in the 21st century and beyond.

(The Institute is grateful to Dr P S Choudhury for reviewing Molecular Imaging in Cancer)

RESEARCH AND DEVELOPMENT

New Leukemia Drug

Leukemia Stem Cells (LSCs) are considered to play a central role in the pathogenesis of acute leukemia and are likely to contribute to both disease initiation and relapse. Therefore, identification of agents that target LSCs is an important consideration for the development of new therapies.

A new report has indicated that scientists could be on their way to creating a new leukemia therapy extracted from a plant known as Fever Few or Bachelor's Button. Dimethylaminoparthenolide (DMAPT) is a modified form of parthenolide. Laboratory studies with DMAPT have shown that it induces rapid death of primary human LSC from both myeloid and lymphoid leukemias and is also highly cytotoxic to bulk leukemic cell populations. Molecular studies indicate the prevalent activities of DMAPT, including induction of oxidative stress responses, inhibition of NF- κ B and activation of p53. The compound has approximately 70% oral bioavailability. The scientists are hopeful that human clinical trials with DMAPT would show that it could be developed as a leukemia therapy by attacking the disease at stem cell level without damaging the healthy blood cells and preventing relapses, which current chemotherapies are unable to do as they do not strike deep enough.

(Blood, Sep 5, 2007)

Overcoming Drug Resistance

A team of scientists at the Children's Cancer Institute Australia for Medical Research has discovered a new insight into a mechanism of drug resistance in non-small cell lung carcinoma (NSCLC). This has important implications for improving the targeting and treatment of a number of cancers which are resistant to the current chemotherapeutic drugs.

The scientists discovered that the β III-tubulin component of the cell's cytoskeleton could play an important role in resistance to a wide range of drugs used to treat lung, ovarian and breast cancers. Increased expression of β III-tubulin has been linked to drug resistance in these cancers. The team showed that blocking the expression of the β III-tubulin gene in NSCLC cells led to an increase in their sensitivity to a range of chemotherapeutic drugs. The results strongly suggest that the β III-tubulin component is responsible for protecting NSCLC cells

from the action of key chemotherapeutic drugs. This is the first scientific evidence for the broader implications of abnormal expression of this protein for improving the treatment outcomes for patients.

(Science Daily, Oct 8, 2007)

Prostate Sensor

Prototype Near Infrared Spectroscopy (NIRS) prostate sensor is being developed by Urodynamix Technologies Ltd. to measure the blood flow in the prostate gland and aid in the diagnosis and localization of prostate cancer and prostate disease during digital rectal examination (DRE). The studies confirmed that this technology was able to quantify and evaluate blood flow in the different quadrants of prostate and potentially aid in the diagnosis of disease by reducing the quantity or improving the accuracy of the biopsies. The key value of this technology would be its ease of use and integration with the existing DRE procedure, which is the frontline screening tool for prostate cancer diagnosis. When used in combination with Prostate Specific Antigen (PSA) test, NIRS prostate imaging technology could significantly increase the sensitivity of DRE towards cancer and other conditions of the prostate gland.

(Medical News Today, Oct 10, 2007)

Re-engineered Human T Cells

A new research has shown that modified T cells can be effective in fighting malignancies associated with B cells (immune cells that produce antibody), such as lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL).

In order to get T cells to recognize B cells, scientists created a gene that encodes for a cell surface protein – an artificial T cell receptor called a chimeric antigen receptor which is designed to specifically bind to CD 19 molecule found on the surface of B cells and B cell cancers. The chimeric gene, formed from active portions of several immune system related genes, creates the chimeric antigen receptor protein called 19-28 z, which does not require other co-stimulatory signals to fully activate the T cells. This research will be helpful for the patients with highly lethal B cell cancers. The results give evidence that the technique will work in humans. When transplanted back into a patient, these engineered T cells could then attack and kill tumor cells bearing the CD 19 protein. This is not found on the surface of bone marrow stem cells, so these modified T cells are reasonably safe.

(Clin Cancer Res, Sep 15, 2007)

NEW TECHNOLOGIES

DIAGNOSTICS

Fecal Immunochemical Test

Researchers have recently shown that a new type of test that uses the fecal occult blood, known as fecal immunochemical test, can detect a high percentage of left-sided colorectal cancers. This disease develops in the large intestine, which includes the colon and the rectum. The cure rates are high when cancer is detected and treated early and fall dramatically once the cancer has spread. Presently, the techniques that are used for screening are Fecal Occult Blood Test (FOBT), sigmoidoscopy and colonoscopy.

Scientists have developed a new type of FOBT known as fecal immunochemical test. This test is more specific than the guaiac test, producing fewer false positive results. Certain types of fecal immunochemical test may also be more sensitive and better able to detect cancers and advanced polyps. To evaluate the performance of the two types of FOBT – a sensitive guaiac test and fecal immunochemical test, researchers conducted a study among 5841 people at average risk for colorectal cancers. The fecal immunochemical test detected 82% of the left-sided colorectal cancers and sensitive guaiac FOBT detected 64%. Fecal immunochemical test had higher sensitivity than the guaiac test. The new test performed well for detecting left-sided colorectal cancer and may be a useful replacement for the guaiac FOBT.

(Journal of National Cancer Institute, 2007)

Genetic Analysis of Sputum

Researchers from Amsterdam recently conducted a clinical trial to explore the potential effectiveness of screening for lung cancer through sputum samples. According to the results presented at the 2007 International Association for the Study of Lung Cancer (IASLC) conference, genetic markers that can be detected in a patient's sputum may aid in the screening process for early diagnosis of lung cancer.

Researchers evaluated two genetic markers and their accuracy in detecting lung cancer. Methylation, a type of molecular marker from two genes was compared between patients with and without lung cancer. Methylation markers detected 50% of the lung cancers.

The markers, however, were accurate 95% of the time in identifying abnormalities as non-cancerous. This high specificity is significant because it could potentially reduce the need for patients to undergo a bronchoscopy following CT scan. The results showed that genetic analysis of sputum samples might contribute to the effectiveness of screening procedures for lung cancer. However, further study is necessary to confirm these findings.

(UFSCC, Sep 9, 2007)

Mammostrat Test

Mammostrat is a new molecular targeted breast prognostic test for breast cancer patients. This prognostic test utilizes five immunohistochemical biomarkers to classify the patient into high, moderate or low risk categories for disease recurrence. The test was developed by Applied Genomics, Inc. The new test, which is performed on the tissue preserved according to standard practice, streamlines the process for patients while providing the accuracy of direct visualization.

Mammostrat test results have been validated using over a 1000- patient sample in North America. Because mammostrat uses traditional immunohistochemistry technology, the test is expected to be significantly less expensive than the existing molecular based prognostic tests for breast cancer.

(Molecular Profiling Institute Inc., Sep 5, 2007)

New Genetic Test for Prostate Cancer

A new genetic test, first of its kind, measures the activity of a gene closely linked to cancer, especially prostate cancer. The standard diagnostic tool is the prostate specific antigen (PSA) test which looks for raised level of a protein in the blood that leaks out of the prostate gland. The new test measures messenger RNA which transfers information from the PCA3 gene. Elevated scores are produced only when prostate cancer is present, making the test highly specific. The test could help doctors to decide whether or not to proceed with the biopsies.

Men with raised PSA but who appear to be cancer free, often have to undergo repeated biopsies to check that all is well, while new PCA3 test could ensure that biopsies are carried out only when absolutely necessary. The ProgenSA PCA3 test, which is licensed in the European Union, costs more as compared to the PSA-test. For this reason, it is unlikely to be used as routinely as a PSA test.

(Medical News Today, Sep 22, 2007)

DRUGS**Ixempra for Breast Cancer**

Ixempra® is a new drug approved by the US Food & Drug Administration (FDA) for the treatment of advanced breast cancer. The indication includes the use of Ixempra as a single agent for the treatment of recurrent, advanced breast cancer in patients who have stopped responding to chemotherapy including Anthracycline, Taxanes and Xeloda® (Capecitabine). Ixempra is also approved for the treatment of advanced breast cancer in combination with Xeloda.

Ixempra is a chemotherapy agent and analog of Etoposide. It prevents or reduces the cancer cells from replicating. Two clinical trials have been done for FDA approval. The first trial that evaluated Ixempra as a single agent included 126 patients with advanced breast cancer and who had stopped responding to treatment with an Anthracycline, Taxane & Xeloda. Anticancer responses with Ixempra occurred in 12.4% of the patients. The second trial compared Ixempra plus Xeloda with Xeloda alone in 752 patients who had stopped responding to Anthracycline & Taxane. Treatment with Ixempra plus Xeloda significantly improved the progression-free survival compared with Xeloda alone in this group of patients.

(Cancer Consultants.com, Oct 17, 2007)

Oral Hycamtin

US Food & Drug Administration has approved an oral capsule formulation of the chemotherapy agent Hycamtin® (Topotecan) for the treatment of relapsed small cell lung cancer (SCLC). SCLC is considered a very aggressive type of cancer and responds well to chemotherapy. Following a relapse, patients often respond to subsequent chemotherapy i.e. usual intravenous (IV) formulation of chemotherapy. However, IV formulation is associated with potential of pain, anxiety and infection.

The clinical trial included 141 patients with SCLC who had received prior chemotherapy. One group of patients was treated with the best supportive care (BSC – care to maintain quality of life and reduce symptoms) and another treated with Hycamtin plus BSC. Patients treated with Hycamtin had a 36% reduced risk of death compared with those treated with BSC and the median survival rate was nearly 26 weeks for the patients treated with Hycamtin compared with nearly 14 weeks for those treated with BSC only.

(GlaxoSmithKline, Oct 15, 2007)

EQUIPMENTS**Laser to Scan Veins**

Researchers from Purdue University have developed a technology to detect tumor cells within the human body by shining a laser on the surface veins and have been able to detect and count the circulating tumor cells. This technology could eliminate the drawing of blood. It is also able to evaluate a much larger volume of blood than what can be drawn from a patient for analysis. By increasing the volume of blood analyzed, the sensitivity of the test could improve.

The technique uses a fluorescent tumor specific probe that labels tumor cells in circulation; when hit by a laser, which scans across the diameter of the blood vessel 1000 times per second, the tumor cells glow and become visible. The technology is able to scan every cell that is pumped through the vessel. Researchers have also developed two labeling agents that attach to different forms of cancer. One label targets ovarian, non-small lung, kidney and endometrial cancer and other targets prostate cancer. The method can detect the cells early in disease development and the test can be conducted frequently.

(Purdue University, Sep 12, 2007)

Revolutionary New Device

The researchers from Georgia Institute of Technology have created an acoustic sensor that can report the presence of small amount of mesothelin, a molecule associated with a number of cancers, including mesothelioma, as they attach to the sensor surface. This technique might work for the detection of nearly any biomarker. Acu Ray™ chip, standing for Acoustic Micro-Array, consists of a series of electrodes deposited on the surface of a thin zinc oxide film which allows the device to resonate or vibrate at a specific frequency when a current is applied.

The researchers coated the sensor with antibodies for mesothelin, a cell-surface protein that is highly expressed in mesothelioma, ovarian cancer, pancreatic cancer and other malignancies. When mesothelin binds to an antibody, the added mass changes the frequency at which the acoustic wave passes between the electrodes on the surface of the device. The device is able to “hear” the pitch change due to nanomolar concentrations of mesothelin binding to antibodies on the chip.

(Science Daily, Sep 22, 2007)

IN FOCUS

ERBITUX® - Cetuximab

Merck Serono Oncology has an ongoing commitment to the advancement of oncology treatment. It is currently investigating novel therapies in highly targeted areas, such as the use of Erbitux® (Cetuximab) in colorectal cancer, squamous cell carcinoma of the head and neck and non-small cell lung cancer. Merck Serono Oncology has also acquired the rights for the cancer treatment UFT® (tegafur-uracil), an oral chemotherapy administered with folinic acid (FA) for the first-line treatment of metastatic colorectal cancer. The company is investigating, among other cancer treatments, the use of Stimuvax® (formerly referred to as BLP25 Liposome Vaccine) in the treatment of non-small cell lung cancer.

Cetuximab is a chimeric IgG1 monoclonal antibody that binds the extracellular domain of EGFR with high specificity and ~ 10-fold higher affinity than its natural ligands, EGF and TGF- α . It has a molecular weight of ~ 154 kDa. Competitive binding of Cetuximab to EGFR prevents ligand-induced phosphorylation of the intracellular tyrosine kinase domain, thus inhibiting activation of the further downstream signaling cascade. Furthermore, binding of Cetuximab to EGFR leads to receptor dimerisation followed by endocytosis and intracellular degradation of the antibody-receptor complex. Consequently, EGFR density on the cell surface is downregulated. Cetuximab might further induce antitumor potential by recruiting Fc-receptor-expressing immune effector cells leading to antibody-dependent cell-mediated cytotoxicity.

Metastatic Colorectal Cancer

Cetuximab is approved in combination with irinotecan for patients with EGFR-positive tumors that progressed on a prior irinotecan-based chemotherapy regimen. The approval of Cetuximab in this setting followed the positive results of the so called 'BOND' (Bowel Oncology with Cetuximab Antibody) study, which was conducted in 56 centers throughout Europe. It compared the efficacy of Cetuximab in combination with irinotecan against Cetuximab alone in metastatic colorectal cancer (CRC) refractory to irinotecan based chemotherapy. A total of 329 patients were randomized in a 2:1 setting to the combination versus the monotherapy arm. Following disease progression in the monotherapy

arm, patients were allowed to switch to the combination arm. This applied to half of the patients in this group. Patients in the BOND study were heavily pretreated: > 80% of patients had received two or more prior chemotherapy regimens. A total of 62.6% had received prior oxaliplatin based treatment, and according to the inclusion criteria, 100% of patients were refractory to irinotecan. The efficacy parameters (overall response rate, disease control rate and time to progression) showed a statistically significant advantage in favour of the Cetuximab plus irinotecan combination arm. Improved treatment efficacy may help increase the rate of hepatic metastatic resection after downsizing of initially unresectable lesions.

Locally Advanced Head & Neck Cancer

More recently, the results from a large, Phase III, international, multicenter study to evaluate the combination of Cetuximab with radiotherapy in locally advanced head and neck cancer patients ($n = 424$) have attracted a great deal of attention. This trial, reported by Bonner et al, is the first large scale study to investigate the efficacy of combining a targeted agent and radiotherapy in this patient group.

The addition of Cetuximab to radiotherapy significantly improved survival and locoregional control (defined as the absence of locoregional disease progression at the scheduled follow-up visits) compared with radiotherapy alone. Median overall survival with Cetuximab plus radiotherapy was 49 months, almost 20 months longer than seen with radiotherapy alone (29.3 months, $p = 0.03$; log-rank test). Similarly, there was a clear advantage for Cetuximab plus radiotherapy over radiotherapy alone in the 3 year survival rate (55% versus 45%, $p = 0.05$). Cetuximab plus radiotherapy was therefore associated with a 26% risk reduction in mortality compared with radiotherapy alone (hazard ratio, HR: 0.74). The median duration of locoregional control after treatment with Cetuximab plus radiotherapy was 9.5 months longer than after radiotherapy alone (24.4 months versus 14.9 months, $p = 0.005$; log-rank test). There was also a clear advantage in the 3 year locoregional control rates ($p < 0.01$). Overall, Cetuximab was associated with a 32% reduction in the risk of locoregional failure compared with radiotherapy alone (HR: 0.68). The results from this large study show that the addition of Cetuximab to radiotherapy results in convincing, statistically significant and clinically meaningful improvements in locoregional controls, overall survival and progression free survival.

COLORECTAL CANCER

Curcumin with FOLFOX

Curcumin (diferuloylmethane) inhibits the growth of transformed cells, has no discernible toxicity and achieves high levels in colonic mucosa. Curcumin in combination with conventional chemotherapeutic agent(s)/regimen may be a superior therapeutic strategy for colorectal cancer.

A study conducted by Patel B B et al showed that Curcumin enhances the effects of 5-fluorouracil and oxaliplatin (FOLFOX) in mediating growth inhibition of colon cancer cells by modulating EGFR and IGF-1R.

Curcumin with FOLFOX produced a significantly greater inhibition of growth and stimulated apoptosis of colon cancer cells. These changes were associated with decreased expression and activation of tyrosine phosphorylation of EGFR, HER-2, HER-3 and IGF-1R as well as their downstream effectors such as Akt and cyclooxygenase 2.

Inclusion of Curcumin to conventional chemotherapeutic agent(s)/regimens could be an effective therapeutic strategy for colorectal cancer.

(Int. J Cancer, Oct 4, 2007)

Interleukin – 8 Key Marker

Interleukin – 8 expression may serve as a useful indicator of poor prognosis and a putative target for the development of drugs in colorectal cancer (CRC) therapy.

Dr Rubie and colleagues from the University of Saarland, Germany, have investigated the expression profile of IL-8 in inflammatory, colorectal adenoma, colorectal cancer and colorectal liver metastases (CRLM). The major findings demonstrated significant IL-8 up-regulation in all and the magnitude of IL-8 expression in surgical CRC tissue specimens correlated with increasing tumor stages and also with the malignant status of the colorectal cancer cells. The investigators showed that IL-8 was significantly higher expressed in CRC tissues compared to the inflammatory and adenoma conditions, suggesting an association between IL-8 up-regulation and the development of CRC. Significant IL-8 overexpression was found in CRLM in comparison to the related primary CRC. Patients with higher risk of

developing CRLM may receive different treatment compared to the patients with a lower risk of developing CRLM.

(World J Gastroenterol, Oct 7, 2007)

New Radioactive Agents

Scientists of John Hopkins (John Abraham & Stephen Meltzer) have developed a potential novel way to fight colorectal cancer, using tiny molecules to deliver radiation inside the cancer cell, unlike the current treatments that bind to the surface of cells and attack from the outside and cause unwanted effects. These molecules are small bits of protein, only 10 amino acid long. By contrast, antibodies used to deliver radiation can be over one thousand amino acid long.

Scientists attached radioactive phosphorous P32 to these peptides to test how well their peptides worked. They designed and tested a variety of P32 peptides on 18 normal and cancerous human cell samples. The most potent peptide, MAS, could bind to adeno carcinoma cells 150 times more strongly than other cell types and transferred inside cells within 2 hours.

P32 also gives off high energy to peptides that can penetrate 5 mm of human tissue. P32 labeled peptide can also find small metastases or recurrences of colon tumors. Images of the body can be taken of the labeled peptides as they bind to the cancerous cell, revealing stray tumor cells.

(Science Daily, Oct 10, 2007)

Tritherapy for Liver Metastases

According to a Phase II study in colorectal cancer patients with non-resectable liver metastases, tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) showed a high response rate. The rate of hepatic resection in patients initially not resectable is attractive and warrants further assessment of this regimen in randomized studies compared to the standard regimen.

In this study, thirty-four patients were enrolled. Response rate before surgery was 70.6%. Twenty-eight patients underwent hepatic resection and nine achieved R (0) resection. The rate of complete remission after surgery was 79.4%. Two years overall survival was 83%. The most frequent toxicities were neutropenia, diarrhea, fatigue etc. Four patients withdrew due to toxicity and no toxic death was observed.

(Cancer Chemother Pharmacol, Sep 28, 2007)

CANCER CONTROL

Chemoprevention: Breast Cancer

Older women looking for a medication to help lower their risk of invasive breast cancer now have another option available to them. The US Food and Drug Administration has approved the drug Evista (raloxifene), for reducing the risk of invasive breast cancer in post-menopausal women with osteoporosis and in women at high risk for breast cancer. It joins tamoxifen as just the second so-called chemoprevention drug to be approved for breast cancer.

Evista is a selective estrogen receptor modulator (SERM) that may reduce the risk of invasive breast cancer by blocking estrogen receptors in the breast. Three clinical trials over the past 10 years found that Evista reduces the risk of invasive breast cancer by 44 percent to 71 percent. The drug should not be taken by pre-menopausal women and women who are or may become pregnant. In addition, the drug should not be taken with cholestyramine or estrogens.

(UPI, Sep 14, 2007)

Exercise and Yoga

A multicenter randomized controlled trial done at the University of Alberta, Canada, has shown that exercise and yoga can improve the quality of life in women with early stage breast cancer. Researchers found that resistance exercise is better than usual care for improving the muscle strength, lean body mass and self esteem. Resistance exercise also provides best chemotherapy completion rate. Researchers speculate that it may cause increase in WBC which could allow chemotherapy treatments to continue on schedule as exercise does not cause any lymphedema or other adverse effects. Aerobic exercise can improve aerobic fitness, self esteem and body fat percentage.

A similar study performed at Albert Einstein College of Medicine, Bronx, is the first study to evaluate the benefits of yoga in an ethnically diverse population of women with breast cancer (primary Hispanic and African-American women). Researchers divided the women into two groups, first group comprising those who had already received chemotherapy or radiation therapy during the study period and the others who had either already completed treatment or did not require it. Results showed that those who took yoga reported more physical,

functional and emotional well being in the group who had already completed their chemotherapy or radiation therapy treatment. Yoga can promote better quality of life by helping the patients to connect with others and feel calmer. Patients who did not take yoga, reported a drop in social well being scores compared with those who took it.

(Journal of Clinical Oncology, Sep 4, 2007)

Pomegranate Juice for Prostate Cancer

Pomegranate juice is rich in phytochemicals, substances that have been shown in laboratory studies to inhibit cancer growth and spread. Researchers are exploring the potential of pomegranate juice to slow or reverse increasing prostate specific antigen (PSA) levels in men who have undergone treatment for localized prostate cancer.

For localized prostate cancer (cancer confined to the prostate gland), surgery and radiotherapy are common treatments. During follow up, an increase in PSA level may be an early indicator that prostate cancer has returned. Currently, there is no standard treatment for recurrent prostate cancer detected by an increase in PSA level only. In a Phase II trial, daily consumption of pomegranate juice resulted in a significant lengthening of PSA doubling time and disease stabilization. Researchers hope to verify those results in a Phase III, double-blinded placebo-controlled study.

(NCI Cancer Bulletin, Sep 25, 2007)

Traffic Emissions and Breast Cancer Risk

Breast cancer is a major cause of morbidity and mortality. In addition to the established risk factors, it has been hypothesized that environmental exposure may also contribute to breast cancer. Traffic emissions are the major source of air pollution in urban areas and they contain many potential carcinogens, e.g. polycyclic aromatic hydrocarbons and benzenes. Studies have found that exposure to traffic emissions may be associated with an increased risk of total childhood cancer and childhood leukemia.

The Western New York Exposure and Breast Cancer (WEB) study examined the breast cancer risk in relation to exposure to air pollution from traffic emissions throughout life. The findings add to the accumulating evidence that early life exposures impact breast cancer risk and provide indication of potential importance of traffic emissions in risk of breast cancer.

(Cancer Causes Control, Nov 2007)

INSTITUTE

CHRISTUS STEHLIN FOUNDATION

Introduction

The Christus Stehlin Foundation at Houston, Texas, USA for Cancer Research was established by Surgical Oncologist, Dr John S Stehlin in 1969 with a specific and urgent mission to find and develop the most effective treatments for cancer today in the shortest period of time.

During the past 31 years, the Christus Stehlin Foundation for Cancer Research and the Stehlin and deIpolyi Oncology Clinic have pioneered some notable firsts which have established their reputation internationally for their pioneering cancer research and treatment.

Some of their accomplishments include:

Partial Mastectomy for Breast Cancer: Christus Stehlin Foundation surgeons in 1970 were among the first in North America to recommend breast conserving treatment on selected cancer patients with a combination of partial mastectomy (lumpectomy) followed by radiotherapy. A 25-year study of breast cancer patients showed that the less radical procedure offered equal survival rates, without the mutilation and severe psychological consequences of breast removal.

Research Limited to Investigations with Human Cancers: Unlike the vast majority of cancer research conducted on tumors arising in laboratory animals, all laboratory work of the Foundation is conducted on cancers removed from the patients.

Development and Use of the Nude Mouse: The Foundation pioneered the development and use of the nude mouse in cancer research, establishing that if an anticancer drug works against a human tumor implanted in the nude mouse, for a majority of time the drug will also be effective in treating the patient from whom the tumor was removed.

Effects of Heat on Cancer: The Foundation researchers were the first to demonstrate the selective sensitivity of the cancer cells to heat. Their initial work was published in 1973. As a result of this research, numerous institutions throughout the world are now investigating the effects of heat on cancer.

Hyperthermic Perfusion: The physicians here were the first to combine heat and chemotherapy (hyperthermic perfusion) for the treatment of patients with advanced

melanomas of the arms and legs, essentially eliminating the need for amputation and dramatically improving the survival rates by 300%.

Psychological Needs: The Foundation was among the first to recognize the importance of addressing the psychological needs of cancer patients. It established a "Living Room" in 1980 as a meeting place for hope, faith, laughter and love where patients could find relief from the hospital atmosphere. The "Living Room" quickly became a prototype for cancer treatment centers around the world.

Liver Cancer Studies: The Foundation conducted one of the largest studies of liver cancer ever reported by a single institution in the medical literature. The study, published in *The Annals of Surgery* in 1988 involved 414 patients.

Regional Intra-Arterial Chemotherapy: The physicians in the Foundation were the leaders in the development of regional intra-arterial infusion chemotherapy, in which large concentrations of anticancer drugs can be delivered directly to the specific organs or areas of the body affected by cancer.

Camptothecin: The Foundation is recognized as one of the international leaders in the development and clinical (human) studies of a new family of anticancer drugs, the Camptothecins. 9-NitroCamptothecin, developed at their research facility, is now in clinical trials at approximately 150 cancer institutions across the United States. The drug has generated much excitement in the medical community.

An additional advantage of the Camptothecin family of drugs is that they can be given orally on an outpatient basis, which should translate ultimately to be a less expensive form of administering anticancer therapy, as contrasted with those drugs that have to be given intravenously either in a hospital or physician's office. Camptothecins can be envisioned as the ultimate anticancer drugs when fully developed.

Future Perspectives

The Christus Stehlin Foundation for Cancer Research has witnessed not only life-saving treatments and research for patients with cancer, but the emergence of a unique working philosophy that has set them apart from other cancer centers in the world. It has earned an international reputation for its pioneering treatment and research programs in the fight against cancer.

CLINICAL TRIALS

Gardasil in Precancerous Lesions

Results presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy from a supportive analysis of two large Phase 3 studies in a generally human papillomavirus (HPV) naive population have shown that the four type (6,11,16,18) cervical cancer vaccine Gardasil protected against pre-cancerous cervical lesions [Cervical Intraepithelial Neoplasia (CIN) 2/3, Adenocarcinoma In Situ (AIS)] caused by ten other cancer causing HPV types, in addition to the virus types directly targeted by the vaccine.

During a mean follow-up of three years after the start of vaccination, Gardasil® prevented 38% of precancerous lesions (CIN 2/3, AIS) caused by the ten HPV types 31/33/35/39/45/51/52/56/58/59 which produce around 16% of cervical cancer in Europe and up to 22% around the world.

Gardasil® provides wider ranging and earlier benefits than the prevention of cervical cancer alone. It helps prevent cervical lesions, vulvar lesions and genital warts which occur much faster than cervical cancer, often within a few months after exposure to the virus. Gardasil® has demonstrated up to 100% efficacy against these and a cross-protective efficacy of 38% against ten additional cancer causing types is a significant extra benefit.

(Medical News Today, Sep 20, 2007)

Multiple Myeloma

The interim analysis result of the large, international Phase III VISTA (1) clinical trial in patients with newly diagnosed multiple myeloma showed that the therapy of VELCADE (Bortezomib), melphalan and prednisone (VMP) demonstrated a highly statistically significant improvement in all efficacy measures, including time to disease progression, complete remission rate, progression free survival and overall survival, compared to melphalan and prednisone (MP) alone.

These results position VELCADE based therapy as a new standard of care for newly diagnosed multiple myeloma patients. The trial randomized 682 patients with newly diagnosed multiple myeloma, ineligible for stem cell transplantation, to receive either VMP or MP, a recognized standard of care in this treatment setting.

Patients were enrolled at 151 clinical trial sites in 22 countries. Side effects of the VELCADE based therapy were manageable.

(Millennium Pharma. Inc, Sep 18, 2007)

Red Blood Cell Booster

In cancer patients with chemotherapy induced anemia, use of red blood cell boosters such as Aranesp (darbepoetin alfa), has been shown to decrease the need for blood transfusion, which has associated risks of infection, rejection and increased medical costs. Because of the adverse health effects reported in some studies, the FDA advises physicians to use the lowest possible dose to avoid transfusions and to use red blood cell boosters only as indicated.

To provide additional information about the effects of Aranesp among patients with chemotherapy induced anaemia, combined analysis of six clinical trials showed that Aranesp reduced the likelihood of blood transfusion without adversely affecting survival or risk of cancer progression. These results were presented at the European Cancer Conference (ECCO 14) on September 23-27, 2007 in Barcelona, Spain.

(ECCO-14 Abstract, Sep 23-27, 2007)

Response to Panitumumab

A study of patients with previously treated metastatic colorectal cancer, treated with Vectibix™ (Panitumumab) benefited only those patients with tumors that lacked mutations in a gene known as KRAS. Vectibix is a new targeted therapy which targets the epidermal growth factor receptor (EGFR) and destroys cancer cells directly while sparing the healthy cells from the side effects of treatment. Cancers that contain mutated forms of the KRAS gene may not respond to anti-EGFR treatments such as Vectibix.

Researchers evaluated information from a Phase III clinical trial to assess the KRAS mutations and response to Panitumumab in patients with previously treated metastatic colorectal cancer to treatment with either Panitumumab plus best supportive care or best supportive care alone. The results showed that Panitumumab appears to be effective only among patients with cancers that lack KRAS mutations. Assessment of KRAS status may help identify those patients who are most likely to respond to Panitumumab.

(UFSCC, Oct 9, 2007)

WATCH-OUT

Key Patents for Cancer Testing

Epigenomics, a cancer molecular diagnostic company headquartered in Berlin, Germany, announced on October 8, 2007 that their core technology Heavy Methyl® for the sensitive detection of methylated DNA, has been granted Europe patent (No. 370691) and US patent (No. 7,229,759). The company used this technology for detecting DNA methylation biomarkers for the early detection of cancer. These biomarkers, when measured in body fluids such as blood plasma or urine, form the basis for cancer screening tests. The most advanced product is a blood test for the early detection of colorectal cancer based on the DNA methylation biomarker Septin 9.

The Heavy Methyl® technology is ideally suited for detecting the circulating, tumor derived DNA in body fluids using tumor specific methylation “fingerprints” as biomarkers. Epigenomics’ patent portfolio of DNA methylation comprises more than 190 patent families (granted patents and patent applications).

(Epigenomics AG, Oct 8, 2007)

Neutropenia Prevention

Neutropenia is a shortage of neutrophils in the blood and a toxic condition that often occurs during chemotherapy. Optimata Ltd, an interdisciplinary science-based company, is developing computerized tools for navigating drug development towards better drugs faster. It has been granted a US patent No. 7,266,483 for a system and method that models granulopoiesis and can optimize drug therapies in order to reduce or prevent neutropenia.

The novel technology comprises a computerized biosimulation system and a computer implemented method for optimizing drug therapies that affect neutropenia. This technology can predict the impact of drug regimens on neutrophil levels in the blood and can be applied to optimize the development of new drug therapies (both monotherapy and combination therapy), so as to alleviate their myelotoxicity; to optimize the development of supportive drug treatment; and to repurpose the existing drugs whose use or development has been limited or discontinued because of toxic side effects.

(Biocompare News, Sep 12, 2007)

New Targeted Drug

Helix Biopharma Corp, a biopharmaceutical company specializing in the field of cancer therapy, has been issued its second DOS 47 patent (US Patent # 7,264,800) by the United States Patent & Trademark Office. The patent describes a method and composition for combining targeted DOS 47 therapeutics with weakly basic chemotherapeutic drugs in adjunct treatment applications. DOS 47 therapy is designed to counteract tumor acidity. Tumor acidity is a property that otherwise makes it difficult for weakly basic chemotherapeutics to penetrate the cancer cells and function effectively.

Helix’s first DOS 47 based cancer therapeutics L-DOS 47 specifically targets lung adenocarcinoma alone and synergistically with selected chemotherapeutic compounds. L-DOS 47 combines Helix’s proprietary DOS 47 new drug candidate with a highly specific single domain antibody, to form a potential new targeted drug product for the treatment of adenocarcinoma of the lung, the most common form of cancer in the world today.

(Helix Biopharma Corp., Sep 17, 2007)

Novel Targets in Cancer

Morris David W (US) and Malandro Marc S (US) have been granted US patent No 2007218071 entitled ‘Novel Therapeutic Targets in Cancer’, published on September 20, 2007.

High throughput analysis of expression of hundreds or thousands of genes can help in the analysis of differential gene expression overtime between tissues and disease states. The object of the present invention is to provide polynucleotide and polypeptide sequences involved in cancer, in particular in oncogenesis. The present invention relates to novel sequences for use in detection, diagnosis and treatment of cancers, especially lymphomas. The invention provides cancer-associated (CA) polynucleotide sequences whose expression is associated with cancer and CA polypeptides associated with cancer that are present on the cell surface and present novel therapeutic targets against cancer. The invention provides diagnostic compositions and methods for the detection of cancer and provides monoclonal and polyclonal antibodies specific for the CA polypeptides. The invention also provides diagnostic tools and therapeutic compositions and methods for screening, prevention and treatment of cancer.

(esp@cenet database, Oct 8, 2007)

GLOBE SCAN

Biomarker for Liver Cancer

Researchers at the Chinese University of Hong Kong have developed a new blood screening technique to detect early stage liver cancer that could help millions. Hepatocellular carcinoma (HCC) is one of the deadliest forms of cancer. Ultrasound and CT scan are expensive for effective mass screening. Screening for alphafetoprotein in blood would miss many potential patients, because the protein is present in 70% of the HCC patients.

To diagnose HCC patients, RASSF1A is a good candidate. This is a tumor suppressing gene but it is found to be present in an altered form, both in HCC and HBV patients. In the HCC and HBV tumor cells, this gene is hypermethylated due to cancer related processes that add methyl groups to portions of DNA within the gene. Due to this alteration, RASSF1A is unable to stop the cells from becoming cancerous. Hypermethylated RASSF1A would make a useful biomarker for HCC.

Chan et al have invented a technique "Methylation-sensitive enzyme-mediated real time PCR" which combines real time PCR with an enzyme that breaks unmethylated DNA apart, so that altered methylated DNA can be separated and quantified in a very sensitive way. Refined technique of detecting hypermethylated RASSF1A offers hope to have a functioning test for hepatocellular carcinoma.

(China: *Medical News Today*, Sep 21, 2007)

Circulating Tumor Cells

A group of scientists from the University of Munich, Germany, have shown that they can detect circulating tumor cells (CTC) in blood before and after chemotherapy treatment. The scientists think that the persistence of CTCs after chemotherapy treatment is likely to be predictive of the likelihood of recurrence of cancer in patients. They would analyze the prognostic value of CTCs in the blood of breast cancer patients. If this proves to be the case, it would open the door to a simple way of monitoring the likely outcome of chemotherapy as well as enabling the scientists to target treatments more precisely.

Previous work on the detection of CTCs in bone marrow has also been shown to have predictive value,

but bone marrow is not easily accessible. It is very much simpler and more patient friendly to take the blood samples for analysis.

(Germany: *ECCO Press Release*, Sep 25, 2007)

Cancer Prevention Strategies

During the National Cancer Research Institute Conference held from September 30 to October 3 in Birmingham, UK, scientists discussed cancer prevention strategies, which would combine maximum benefit with minimum side effects for society that could only be achieved with focused research and well designed collaborative clinical trials.

Cancer incidence is increasing and the cost of caring for patients with established malignancies is causing major strains for all healthcare systems. Many lifestyle changes and putative chemopreventive agents have been identified as having the potential to modify cancer risk. There is an urgent need to identify surrogate biomarkers which could help to predict efficacy. The increasing understanding of the biological changes associated with carcinogenesis have led to the development of cancer strategies based on the use of targeted agents to delay or prevent the development of malignancy.

(UK: *NCRI UK*, Oct 2, 2007)

New Drug Paradigm

A collaborative effort between the laboratories of Kent State University, Summa Health System and IC-Medtech Inc, has culminated in two patent applications for drugs that show promise for treating cancer, herpes and other diseases, based on the pharmacologic properties of liquid crystals. The group filed applications for a liquid crystal pharmaceutical (LCP)-based anti-tumor drug called tolecine and another for a formulation that combines Tolecine and another LCP called Apatone. Already, apatone has been granted orphan drug status by the FDA (August 2007) for the treatment of metastatic, or locally advanced inoperable bladder cancer.

LCPs are an untapped frontier from which many new, exciting treatments are now emerging. Unlike other chemotherapeutic drugs, Tolecine and Apatone have low toxicity and do not target dividing cells. They provide new hope in the battle against cancer and other diseases in the next few years.

(US : *Kent State University*, Sep 6, 2007)

ACTIVITIES OF RGCI&RC

Helical Tomotherapy

A team from Tomotherapy Incorporated USA delivered a presentation on "Tomotherapy and IGRT" on October 1, 2007 in the Conference Hall, Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC), Delhi. It was attended by Dr. K.V. Swaminathan, Chairman, Mr. K K Mehta, Hon'y Secretary, Senior Consultants, Medical Physicists and Doctors of Radiation Oncology Department of RGCI&RC.

Professor Negi, Chief Medical Physicist, RGCI&RC, welcomed Dr Gustavo Olivera, Vice President of Research, Mr Sandeep Jaswani and other members of the team. Prof Negi stated that Helical Tomotherapy represents the next generation of cutting edge radiation therapy technology. The technique is a hybrid between a linear accelerator and a helical million volt CT scanner designed for the purpose of delivering highly conformal intensity-modulated radiation therapy (IMRT). Dr Gustavo Olivera discussed the present and future aspects of this technology and Mr Jaswani presented the planning and physics aspects as well as the benefits of the technology.

Concept and System

Image-guided IMRT is a revolutionary concept whose clinical implementation is rapidly evolving. Tomotherapy Research Centre of the University of Wisconsin, Madison, Wisconsin USA has developed helical tomography as an innovative solution to overcome some of the limitations of other IMRT systems.

The tomotherapy system uses hundreds of pencil beams of radiation spirally rotating around the tumor, focusing it from all directions. Using these dynamically rotating beamlets, each varying in intensity, oncologists can now deliver radiation with un-precedented precision. The high dose region of radiation can now be shaped to fit the exact shape of each patient's tumor. It can adjust for day to day change of the patient's position and internal motion of the target to further improve the precision of treatment delivery.

The imaging capacity conferred by the CT component allows targeted regions to be visualized prior to, during and immediately after each treatment. The intrinsic

capability of helical tomotherapy for megavoltage CT (MVCT) imaging for IMRT image guidance has been optimized. The MVCT images supplant the port-films used in conventional radiotherapy, providing unprecedented anatomical details. Image-guidance through MVCT allows the development and refinement of the concept of "adaptive radiotherapy", the reconstruction of the actual daily delivered dose accompanied by prescription and delivery adjustments when appropriate. Another unique feature is that helical tomotherapy appears capable of further improvement over 3-dimensional conformal radiation therapy and non-helical IMRT in the specific avoidance of critical normal structures i.e. "conformal avoidance," the counterpart of conformal radiation therapy. These advances improve normal tissue sparing and permit dose reconstruction and verification, allowing significant biological effective dose escalation, biological findings, can be translated into altered fractionation schemes.

The tomotherapy system has broad applicability to many forms of cancers of variable shapes and sizes. The team presented examples of cases of treatment of tumors of head & neck, breast, prostate, brain, lung, oesophagus, rectum, anal canal, etc. Various examples of highly complex treatment plans, such as those involving total lymphatic irradiation, total marrow irradiation, multiple brain metastasis, total scalp irradiation, bilateral breast/chest wall irradiation were also presented. It also has useful applications in pediatric tumors due to better sparing of the normal organs which are more sensitive to radiation than in adults. It can treat whole craniospinal axis in continuity due to its large field size and helical dose delivery. It was emphasized that tomotherapy alleviates the need for multiple fields thereby avoiding errors in dosimetry at the field junctions. It allows for faster treatment delivery with greater accuracy than the other currently available conformal radiation therapy techniques. The feasibility of organ motion related tomotherapy delivery was also discussed.

This cutting edge radiation therapy technology became functional in 2003. At present, there are 150 clinical systems operational across the world, including USA, Europe and Asia Pacific. In India, Tata Memorial Hospital has recently installed a tomotherapy facility. Tomotherapy Inc, in partnership with its distributors in India, has set up a facility for maintenance services, troubleshooting and spare parts in Bangalore and plans to set up various support and maintenance centres across the country.

Home Cancer Care Meet

Rajiv Gandhi Cancer Institute & Research Centre's (RGCI&RC) Home Care team organized its fourth get-together for the families of cancer patients on October 6, 2007. It was aimed to afford them an opportunity or a platform where they could express themselves emotionally and also share their experiences and concerns with each other. This get-together was very successful in bringing them close to each other.

RGCI& RC started the Home Cancer Care Service for the terminally ill patients in October 1997. As part of the programme, a physician, a nurse and a clinical psychologist visit the terminally ill patients at their respective homes and provide them medical, nursing and psychological support at regular intervals along with free medicines and nutrients.

The main objectives of the get-together were:

1. To introduce face-to-face all the families who are/were facing similar crisis in caring their patients at home.
2. To provide them a place where 'cancer' and people suffering from it can discuss it freely with each other without any stigma.
3. To encourage emotional catharsis and share feelings among themselves.
4. To seek sources of support/inspiration from each other within the group.
5. To make an effort to bring out a degree of positive attitude in the lives of all those attending the meeting.

On the whole, the get-together was successful in meeting the above mentioned objectives. It was attended by around 30 people (23 families). Some of the old patients, attendants were a source of psycho-social support for the others. All of them shared their experiences, feelings and emotions.

The programme started with 'Introduction of Home Cancer Care Services' by Dr Sunil K Khetrpal, Medical Superintendent, RGCI&RC. Dr AK Chaturvedi (Medical Director) and Mr KK Mehta (Hon'y Secretary) also addressed the gathering.

During the session, a 2-minute 'silence' was observed to pay homage to the departed patients. It was followed by an interactive session in which Dr Chaturvedi and

Mr Mehta answered the questions of the attendants. The role of alternative medicines was also discussed. One of the attendants (a lawyer) promised to offer free services to RGCI & RC.

An important suggestion in the gathering was to conduct awareness programmes about cancer in public and government schools and also in the universities and colleges, as it was thought that the students could help in creating more awareness and aid in many ways, i.e. blood donation and in cancer checkup camps.

All the attendants highly appreciated the services given by the Home Care team and expressed their gratefulness towards them. It was suggested that this service should be continued and expanded further. All the participants were happy and satisfied. They expressed their desire to attend many more such sessions in the future also.

Dr Rajni Mutneja from Home Cancer Care Service concluded the session and thanked all the participants and guests for their presence.

CME on Chronic Myeloid Leukemia

A one-day CME on Chronic Myeloid Leukemia (CML) was organized by Rajiv Gandhi Cancer Institute & Research Centre along with Association of Physicians of India, Delhi Chapter on October 7, 2007 at India International Centre, Delhi. This CME was attended by more than 100 general physicians, budding oncologists and oncology specialists of the city.

There were three brain storming sessions, covering almost every aspect of diagnosis and the day to day management issues of CML. The initial introduction about CML was given by Dr Vinod Raina, Prof and Head of Medical Oncology, AIIMS; Dr Vaimrsh Raina from Apollo Hospital covered the diagnostic aspects of CML. Dr Rajat Kumar of AIIMS dealt with the general aspects of treatment with wonder drug Imatinib. The role of newer tyrosine kinases in CML was touched upon by Dr Shyam Agarwal from Ganga Ram Hospital. Dr Lalit Kumar from AIIMS explained the role of bone marrow transplantation in CML in the Imatinib era.

The brain storming sessions were followed by a panel discussion on the management difficulties in CML. Panelists included Dr Velu Nair, Dr Dinesh Bhurani, Dr Dharma Chaudhari & Dr Jyoti Kotwal. Session was moderated by Dr Vineet Talwar. All attendees actively participated in the panel discussion.