

### *Editorial*

This is the second issue of the Cancer News and another step in the war on the dreaded killer Cancer. The major burden of cancer is placed on the older population. Elderly cancer patients are under-presented in cancer services utilization and clinical research in India. National data on provider's knowledge, attitude and approach with regard to elderly cancer patients is sparse and urgently needs strengthening to address the needs of this vulnerable and growing population. With this theme in mind the Special Feature in this issue of the **Cancer News** highlights the problem of cancer in the elderly.

Proteomics in Diagnostics described under 'Perspective' explains how it can accelerate the progress towards novel diagnostic and predictive tools to track early disease and tailor treatments to specific patients.

In addition, it has also touched upon some important features such as 'Watch-Out' and 'Global Scan'. Lpath Inc's recently patented anticancer drug 'Sphingomab' may represent the next generation of anti-angiogenesis based therapeutics. Identification of the composition of human telomerase – an enzyme integral to 85% of all cancers, is a breakthrough discovery which would speed up the process of delivering successful treatment.

RGCON-2007, the 6<sup>th</sup> International Conference on 'Cervical Cancer – Current Managements and Future Directions' covered most of the aspects related to the prevention, screening and early detection of cervical cancer so important for women of developing countries like India. A special report on the conference has also been incorporated in this issue.

Cancer News, a bimonthly publication, is a new initiative of the Rajiv Gandhi Cancer Institute & Research Centre. It would focus on research in the field of cancer and modern trends for its early detection, prevention and treatment. It is aimed at sensitizing and benefiting targeted groups of people like researchers, clinicians, academicians, students, etc. It will disseminate the latest global advancements on cancer, nationally and internationally. We welcome your views and suggestions which would greatly help us improve its contents and coverage and win the fight against cancer.

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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 **RGCI&RC**.

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## SPECIAL FEATURE

### CANCER IN THE ELDERLY

#### Introduction

Cancer is a disease of the aging, and aging of the population has been a major factor in the increased incidence of cancer during the last five decades. According to Lodo-vico Balducci of USA, 50% of all malignancies occur in the 12% of the population aged 65 and above. By the year 2030, when the elderly are expected to represent 20% of the entire US population, 70% of all malignancies will occur after the age of 65.

Cancer risk increases with age as a result of cumulative genetic, molecular and biological changes. In most affluent nations, great progress in the prevention and treatment of infectious and childhood diseases has led to increase in the longevity, but such gains have come with an increase in the number of people with cancer. The greatest burden of cancer occurs in men and women aged 60 years and older, a population that suffers excess morbidity, reduced quality of life and economic disparity due to chronic disease.

Until recently, cancer in the elderly received little attention. Shifting demographics, major advances in medical treatment and improved health and longevity in persons past middle age have led to a gradual transition from a palliative approach to disease management, to an emphasis on curative treatment. Moreover, prevention and risk reduction for many cancers is now feasible. The awareness of the burden of cancer among elders has led to increased research and support care. New trials focussing on the elderly, which include detailed functional and quality of life assessments, are now in progress. Data from clinical trials is mandatory for providing optimal care to the elderly with cancer, and for factoring in the effects of comorbidity and loss of function on cancer treatment. Thus treatment and management of cancer in the elderly addresses major and fundamental issues and problems encountered in delivering cancer care to the elderly patients.

Treatment and accrual of elderly cancer patients in clinical trials in India is far from optimal. According to a study conducted by Arora et al (2006), Geriatric oncology exists in 5% centers in India. He also observed that 75% of elderly patients receive some therapy, only 50% of potentially curable patients and similar percentage of potentially incurable patients receive standard care.

50% patients require modification in their treatment and also two-third of treated patients complete therapy. The barrier to treatment included poor performance status (53%), advanced stage (16%) and comorbidities (15%). Standard of care and evidence based recommendations for elderly patients were felt to be lacking by 49% and 92% of the respondents respectively.

#### Epidemiology of Cancer and Aging

Of special interest are the emerging epidemiology of some of the malignancies in the elderly, changes in the epidemiology of lung and cervical cancer, the stage at presentation of cancer in elderly and multiple malignancies.

Aged represent a natural monitoring system for new environmental carcinogens. Older organisms contain a higher number of cells in advanced carcinogenesis than younger organisms and are more susceptible to the action of environmental carcinogens. Lung cancer is becoming a disease of the elderly and also the prevalence of more indolent forms of lung cancer is increasing with smoking cessation at middle age. This evolution may warrant the study of prevention and adjuvant treatment of lung cancer in elderly ex-smokers. Incidence of cervical cancer decreases after the age of 40, the risk of cancer related deaths seems to increase with age. Etiology, pathogenesis and screening are important aspects for this disease to be considered. Breast cancer may become more indolent with age, and is more likely to present at an advanced stage in older women. In about 10% of cancer patients aged 70 and above, a second or even a third malignancy is observed, which involves new decision related both to prevention and treatment.

#### Aging and the Natural History of Cancer

Age is a marker of underlying and only partially defined biological phenomenon that may influence cancer behaviour. The mechanisms responsible for these changes involve either the neoplastic cell (the seed of cancer) or the tumor host (the soil where the cancer grows). Acute myelogenous leukemia is more resistant to chemotherapy in older individuals due to a seed mechanism. Breast cancer becomes more indolent with age, due to a combination of seed and soil mechanisms. Neoplasms whose prognosis changes with age include non Hodgkin's lymphoma and ovarian cancer for which the prognosis worsens, and non-small cell lung cancer, for which it may improve.

### Assessment of the Older Persons with Cancer

Functional status, depression, cognitive impairment, nutritional status and insufficient social support have all been demonstrated to affect the survival of elderly cancer patients, with relative risks of death often increased two to four times. The most effective evaluation of the clinical importance of functional limitations and disability is provided by the Comprehensive Geriatric Assessment (CGA). Areas of assessment include: demographic, health function, cognition, emotions, nutrition, social and economic status.

A reliable assessment of co-morbidity is also essential in elderly cancer patients to establish the benefits and risks of specific antineoplastic agents and to grossly estimate survival. The prognostic impact of associated diseases may be different according to their severity.

**Physiological Changes in Elderly :** The fear of exposing the elderly patients to increased toxicity, morbidity and mortality rate can be minimized by improving our insight at physiological aspects of geriatrics. The progressive functional inadequacy of physiological system is variable in individuals. It has significant impact in the peri-operative management of cancer patients, as well as tolerance to oncological treatments i.e. chemotherapy, radiotherapy, and major curative surgery.

**Cardiovascular System:** Reduced distensibility over stressed heart could impair coronary perfusion and hence lead to cardiac ischemia, depletion of intravascular volume, impaired response to catecholamine and increased myocardial relaxation time and thus adversely affect the functioning of elderly patient under stress. Cardiac arrhythmia and conduction abnormalities increase with aging.

**Respiratory System:** Reduced lung elastic recoil with increasing chest wall stiffness results in decreased compliance and increased functional residual volume. As per literature, 9-18% elderly patients suffer from respiratory complications during postoperative period after major noncardiac and thoracic surgery.

**Body Composition:** Changes in body weight, total body water, body fat distribution and muscle mass may affect response to drug therapy and anaesthetic drugs. This along with decreased renal clearance accounts for higher plasma levels of water soluble non-depolarising muscle relaxants in the aged.

**Fluid, Electrolyte and Renal Physiology:** Hemostatic reserve decreases with age. Elderly become dehydrated and acidotic.

**Liver Function:** There is decrease in plasma albumin concentration. Wound healing in elderly presents a major clinical and economic problem.

### Biological Features of Cancer in the Elderly

Aging alters the biology of cancer. These biological changes affect the risk of cancer, tumor activity and the response to treatment. Age plays a different role according to each specific cancer type. For several tumors, most notably breast, prostate and lung cancer, there is good evidence that the tumors may be different. A difference in the growth pattern and doubling time, hormonal receptor status, DNA ploidy, angiogenesis, percentage of cells in S phase, p53 expression, extra cellular matrix proteins expression, has been noticed and confirmed.

### Targeting Treatment

A decision-making process on how best to treat the elderly cancer patient is quite complex; it requires a careful evaluation of different variables that might affect the final result.

*First step* - patient age, performance status, activities of daily living/instrumental activities of daily living, CGA.

*Second step* - cancer-biologic characteristic, stage, symptoms and therapeutic options.

*Third step* - target-life expectancy, quality of life.

*Fourth step* - Final decision - treatment (standard, tailored), palliative supportive therapies.

All specialists concerned, patient and family should be involved in the decision-making process.

### Role of Various Modalities of Treatment

Although the risk for surgery increases in the elderly with comorbidities, there are ways to evaluate risk to allow interventions that might potentially decrease morbidity and mortality. Appropriate treatments should be offered to the elderly until studies are performed that demonstrate that the elderly can safely be managed in a different manner than younger patients. The elderly should not be denied adequate treatment simply on the basis of age alone.

Radiation therapy plays an important role in the treatment of the elderly oncologic patient. It is believed that elderly are at high risk for the development of acute

and chronic radiotherapy (RT) sequelae. In fact, age per se should not be used as a reason to withhold definitive or palliative RT. Treatment decision should instead be based on the general health and performance status of the patient. Novel RT approaches and techniques are appealing in the elderly, particularly for those unfit for extensive surgery and/or chemotherapy. Radiation therapy also offers the elderly patient effective palliation when cure is not possible. Further research is needed to define clearly the role of RT in this important and growing group of patients.

Chemotherapy has demonstrated beneficial effects in the treatment of cancer, but it has principally been studied in patients under 65 years age. Elderly patients have frequently suffered from many of the toxicities. It is hoped that advances in supportive care will provide improvements in the toxicity to the therapeutic ratio of chemotherapeutic drugs. With appropriate administration and monitoring, it can be used effectively for elderly cancer patients in adjuvant, curative as well as palliative settings.

### Supportive Treatment

Aging is associated with a progressive decline in the functional reserve of multiple organ systems, which may lead to enhanced susceptibility to stress such as that caused by cancer chemotherapy. Myelodepression is the most common fatal complication of chemotherapy. Malnutrition can be due to the malignancy to the patient himself and to the cancer treatment. Anaemia is the second most important factor affecting treatment and prognosis of cancer patients. Fatigue is a common symptom affecting quality of life after pain. Caloric intake should be at least 5-6 meals per day. For chemotherapy related anaemia, erythropoietin should be supported by folic acid and vitamin B12 administration. Hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) are recommended in a prophylactic setting during standard chemotherapy such as CHOP or CMF. ASCO warmly recommend broad-spectrum cytoprotective agent amifostine in preventing platinum-induced nephrotoxicity and mucositis in head and neck cancer patients treated with radiation therapy. Amifostine can also accelerate the hemopoietic recovery.

### Training in Geriatric Oncology

Increasing age is a risk factor for cancer and cancer deaths associated with changes in tumor biology. It generates novel and unique decisional

issues related to cancer prevention and treatment, clinical research, including the diversity of older patients, and the recruitment of these patients into clinical trials. It requires special training in the assessment of older individuals of the quality of their life during treatment and, perhaps more important, during survival. Educational needs related to aging are required. Irrespective of the most functional care health, it is encouraging to find that the interaction between aging and cancer are being investigated and a solution for this problem is being sought.

### End-of-Life Care

Elderly, terminally ill patients require a unique and specialized approach to end-of-life care. A multidisciplinary team should be assembled to care for these patients, given the multifaceted and complex care they require. Special attention to early recognition and intervention for pain and depression needs to occur. Elderly patients are more vulnerable to toxicities of medication, and certain medications should be avoided. Patients and their physicians need to discuss realistic treatment options in the language that is realistic, compassionate and easy to understand. Terminally ill patients would like to be cared for in long term care facilities like Hospice, at the end of their lives. Patient and family would desire to discuss this matter with their physician.

### Conclusion

The time-bomb of the elderly patients soon likely to represent the largest proportion of cancer subjects, is ticking fast. Increased attention to this problem has been seen over the last few years, together with the holistic aspects that it implies. Large funds are needed to provide them the most appropriate specific and supportive treatment, with the two-fold target: optimizing quality of life and increasing life expectancy. Forthcoming gene and biological therapies would be appropriate for elderly cancer patients; there are expectations for them to largely replace conventional chemotherapy. An integrated and targeted multidisciplinary treatment plan is nevertheless required for now, in keeping with the disease complexity. Each different stage of the disease in each patient requires the harmonization of diversified experiences, with respect to cancer progression, patient health conditions and quality of life.



## PERSPECTIVE

### PROTEOMICS IN DIAGNOSTICS

#### Introduction

Proteomics involves the systemic study of proteins which represent the functional output of a cell. They reflect the true status of a cell and differential protein expression may help define healthy from diseased status. Researchers and scientists are working on developing a map of the human proteome that identifies novel protein families, protein interactions and signaling pathways. Current research is looking at protein families linked to diseases, including cancer, diabetes and heart diseases.

Proteomics is at the forefront of cancer research and clinical investigation. Proteomic technologies provide the means to define and compare protein profiles in normal and pathological samples, correlate protein profiles with biological activities, define disease mechanisms at a molecular level, establish interrelationships among proteins, identify temporal pattern of expression and define the function of uncharacterized proteins. As a result, there is intense interest in applying proteomics to fasten a better understanding of cancer processes, develop new biomarkers for diagnosis, early detection, prediction and prognosis of cancer, identify tumor antigens recognized by the immune system, discover new molecular targets for accelerated development and identify markers for therapeutic efficacy, toxicity and patient stratification leading ultimately to better management of cancer patients.

#### Biomarker Profiling in Cancer

Most of the functional information of cancer associated genes reside in the proteome which is an exceptionally complex biological system involving several proteins that function through post translational modifications and dynamic intermolecular collisions with partners. These protein complexes can be regulated by signals emanating from cancer cells, their surrounding tissue micro-environment and/or from the host. Some proteins are secreted and/or cleaved into the extra cellular milieu and may represent valuable serum biomarker for diagnostic purposes. It is estimated that the cancer proteome may include over 1.5 million proteins as a result of post translational processing and modifications. Such complexity clearly highlights the need for robust quantitative protein measurements and data acquisition.

#### Techniques

Proteomics encompasses a broad array of techniques. Bodily fluids (serum, urine, ascites) and tissues are complex mixtures of proteins that may require separation for further analysis. One of the most common technique, though of low-resolution, is simple two-dimensional polyacrylamide gel electrophoresis (2DE). Mass Spectrometry (MS) is a leading technology for high throughput analysis of expressed tissue or biofluid proteins. Coupling MS with Matrix Assisted Laser Desorption Ionization (MALDI) is one high throughput method by which proteins can be identified. The use of tandem mass spectrometers (MS – MS) allows a more detailed determination of peptide sequences. Surface Enhanced Laser Desorption Ionization (SELDI) with Time Of Flight Mass Spectrometry (SELDI-TOF-MS) has increased in popularity, especially in the examination of clinical samples. SELDI, like MALDI, is linked to an automated high-throughput system and can examine low-molecular-weight peptides and proteins.

#### Clinical Applications

- i. Serum proteomics:* MS and other advancing proteomic techniques are being applied to identify serum protein biomarkers or profiles or protein signatures of specific disease status or phenotypes.
- ii. Urine proteomics:* Urine provides an alternative source to blood for the detection of potential biomarkers. Urine proteomics is an attractive technique because it is non-invasive and can be collected easily.
- iii. Cerebro-spinal fluid (CSF):* CSF protein increases with most brain diseases, leaving the CSF as a possible rich source of proteomic information. The evaluation of CSF may prove to be useful in neuro-oncology.
- iv. Tumor specimen analysis :* Tissue proteomics has the potential to be a powerful new tool in the diagnostic armamentarium, as proteins are the effectors of the molecular aberrations that cause cancer.

#### Future Perspectives

Current clinical and pathological markers poorly predict early disease development and response to treatment. Standard diagnostic methods, including tissue histopathology are now shifting rapidly towards molecular diagnosis due to the rapid progress in proteomic instrumentation. This powerful technology can identify all proteins and their post translational modifications in diseased conditions and hence will greatly accelerate the progress towards novel diagnostic and predictive tools to track early disease and tailor treatments to specific patients.

## RESEARCH AND DEVELOPMENT

### Exciting Discovery

Researchers from Massachusetts have identified a member of the tumor necrosis factor receptor superfamily, TROY, which may represent both a biomarker and therapeutic target for melanoma. Genetic screening detected cDNA encoding TROY. TROY may provide hope for a reliable and sensitive melanoma blood test and may finally become a clinical reality. Additionally, TROY presents an exciting new target for therapy that is currently missing. The researchers found that none of the 10 normal skin biopsies and none of the 6 basal cell carcinoma specimens had detectable TROY expressions, but all 45 primary and metastatic melanoma patient samples were TROY-positive with high levels of cytoplasmic expressions in individual tumor cells. Thus identification of TROY is truly an exciting discovery in the fight against melanoma. With TROY, now there is a new target on Melanoma to attack the disease directly rather than indirectly.

*(Onco Link Cancer News, Apr 5, 2007)*

### Inflammation Triggers Metastasis

According to the researchers, inflammation associated with the progression of tumors plays a key role in the metastasis of prostate cancer. They have shown that proteins produced by inflammatory cells are the 'smoking gun' behind prostate cancer metastasis. They observed that a protein kinase called I $\kappa$ B kinase (IKK $\alpha$ ) turns down the expression of a single gene called Maspin, which has well-established antimetastatic activity in breast and prostate cancers. They found that the production of Maspin is repressed by a series of events triggered by tumor inflammatory cells, with the result that prostate cancer cells spread. They detected an excellent inverse correlation between IKK $\alpha$  activation and Maspin production. The researchers have discovered a signaling pathway that increased metastasis. The pathway is activated by a ligand that binds to a receptor that activates nuclear factor Kappa -B (RANK). RANK ligand, produced by inflammatory cells that invade advanced prostate tumors, triggers a chain reaction in which IKK $\alpha$  is activated, allowing it to enter the nucleus of the cancer cell, repressing Maspin. Interference with

RANK ligand production or activation, as well as interference with IKK $\alpha$  activation, may offer new therapeutic strategies for the prevention of metastatic disease.

*(Science Daily, Mar 19, 2007)*

### Mini-Molecules Up, Cancer Genes Down

New research shows that All-trans-retinoic acid (ATRA), a gold standard drug for treating acute promyelocytic leukemia, turned mini molecules called microRNAs up and cancer genes down in the leukemic cells. ATRA raised the levels of miRNA - 15b, miRNA - 16-1 and let - 7 in leukemia cells which coincided with a fall in the activity of two important cancer causing genes. miRNA - 15b and miRNA - 16-1 reduced the activity of the Bcl-2 gene which is over-active in many kinds of cancers. The protein produced by this gene blocks the normal process of cell death and helps keep cancer cells alive long after they should have died. miRNA let - 7 lowered the activity of the Ras oncogene, an important cancer causing gene. The findings showed that ATRA induced the expression of these three miRNAs and through them regulated genes that need to be silenced for the cells to differentiate.

*(Ohio State University, Mar 5, 2007)*

### To Image and Then Destroy Cancers

The researchers screened 2700 agents until they hit upon Velcade, targeted chemotherapy for multiple myeloma, to induce the lytic cycle within the Epstein-Barr Virus (EBV) to make it replicate within the tumor cells expressing EBV's thymidine kinase (EBV - TK) enzyme in the EBV. Once TK activated, an injection of radiolabelled chemical (FIAU) made it easy to image the tumors with virus in them, using a gamma camera. According to researchers, FIAU not only lights up the tumors, but could also potentially kill them. For imaging FIAU can not only carry a radionuclide that emits a low energy gamma photon, but can also be engineered to carry therapeutic radionuclides, which are lethal to cells in which TK is activated. This strategy could offer a novel way of treating many cancers associated with EBV, including at least four different types of lymphomas and nasopharyngeal and gastric cancers.

*(Amer. Assoc. for Can. Res, Feb 28, 2007)*

## NEW TECHNOLOGIES

### Cancer-Killing Atomic Laser

Scottish scientists propose cancer-killing atomic laser, a laser capable of destroying cancer cells using nuclear energy. The team is optimistic that such a technology could allow thousands of people with cancer to benefit from the latest innovations in medical care. The team would be working to produce smaller and more cost-effective machines, thereby allowing a greater number of cancer patients to be treated with this method. Proton therapy allows energy to be released in a short, concentrated burst, with the protons passing through skin and tissue before releasing their energy to kill the cancer cells. The new technology will minimise the added risk to patients and allow doctors to target tumors in problematic places, including near the spinal cord and behind the eye.

*(Cancer Research UK, Apr 3, 2007)*

### Contrast Agent Targets Breast Cancer

Scientists have developed a contrast agent that selectively targets and highlights malignant micro-calcifications in the breast, while ignoring similar micro-calcifications found in benign breast conditions. The new agent works by binding to micro-calcifications produced in breast cancers. Calcifications in malignant breast tumors contain hydroxyapatite. The contrast agents are designed using a combination of bisphosphonate, with a near-infrared fluorophore. When used with optical tomography, doctors can reconstruct a three-dimensional image of tissues deep inside the breast, highlighting areas where malignant tumors appear. The agent may also be used during surgery to pinpoint the location of hydroxyapatite, and therefore the breast cancer cells themselves. When used with a non-invasive imaging method, the contrast agent could diagnose disease within minutes and determine where biopsies are needed. This approach may monitor women with dense breast tissue or high risk women for developing breast cancer. For screening, this approach may supplement mammography for catching more cancers than mammography alone.

*(American Chemical Society, Mar 26, 2007)*

### Immunochemical FOBT

The newer type of Fecal Occult Blood Test (FOBT), known as an immunochemical FOBT,

performs better than older approaches to FOBT in the detection of colorectal cancer and colorectal polyps. According to the researchers, this test is more specific than the guaiac-based test as it produces fewer false-positive results, and certain types of immunochemical FOBT may also be more sensitive (better able to detect cancers and advanced polyps). In the current study, researchers in Israel compared the results of a quantitative immunochemical FOBT with the results of colonoscopy. During colonoscopy, cancer was identified in 17 study participants and advanced colorectal polyps were identified in 74 study participants. Among the study participants with cancer or advanced polyps, the immunochemical FOBT correctly classified 67% as positive. Among the study participants without cancer or advanced polyps, the immunochemical FOBT correctly classified 91% as negative. Thus this test performed well in the detection of colorectal cancer and advanced colorectal polyps. This study included many patients at particularly high risk of colorectal cancer. However, it is uncertain how the test will perform in the general population.

*(Annals of Internal Medicine, Mar 8, 2007)*

### Rapid Assay System

Results from a multicentric prospective study of a rapid assay system for analyzing Sentinel Lymph Node (SLN) biopsies report that new technology for conducting genetic assays may lead to more accurate intraoperative evaluation of SLNs in patients with breast cancer. The system is based on the GeneXpert Polymerase Chain Reaction (PCR) instrument, a self-contained, single-use-cartridge system developed by Cepheid Inc. The system is both simple to operate and fast. It can deliver results in less than 30 minutes from the time a sample is delivered to the lab. SLN samples were assayed by standard haematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) as well as with the GeneXpert system. The company provided cartridges for detecting 3 genetic cancer markers. The overall results with GeneXpert closely matched those of the H&E and IHC testing. Results of GeneXpert are totally objective and no pathologist opinion is needed to interpret the findings. Overall the GeneXpert successfully produced results in the 97.3% of runs.

*(Doctor's Guide, Mar 20, 2007)*



## NEW TREATMENT

### Breakthrough Vaccine

Cancer Treatment Centers of America has announced its plans to launch a new cancer vaccine therapy that expands treatment options for thousands of women with advanced stage ovarian cancer. This vaccine therapy presents a promising new chapter in the fight against this devastating disease.

The breakthrough treatment method uses the patient's own tumor tissues to create a patient-specific vaccine and is combined with chemotherapy delivered directly into the abdominal cavity. Ovarian cancer, one of the hardest cancers to detect in the early stages, is a very complex disease that is often resistant to chemotherapy. Cancer Treatment Centers of America will offer this new treatment to patients whose cancer has recurred after chemotherapy.

*(Biocompare, Mar 8, 2007)*

### Radioactive Microspheres

Microspheres that contain a radioactive substance along with the chemotherapy regimen FOLFOX4 (5-fluorouracil, Eloxatin, Leucovorin) provide substantial anticancer activity to patients with colorectal cancer that has spread to the liver. Radioactive microspheres are small spheres that contain radioactive material. These are injected into vasculature of the liver, where they tend to get lodged in the vasculature responsible for providing blood and nourishment to the cancer cells. While lodged in place, the radioactive substance spontaneously emits radiation to the surrounding cancerous area while minimizing radiation doses to the healthy portions of the liver. The researchers conducted the clinical trial to evaluate the effectiveness of radioactive microspheres including Yttrium – 90 in addition to FOLFOX4 and concluded that with a median time to cancer progression within the liver of over one time, the trial provided impressive anticancer responses among patients with inoperable liver metastasis from colorectal cancer.

*(UFSCC News, Mar 21, 2007)*

### Sunitinib for Kidney Cancer

Research has shown the efficacy of a pharmaceutical drug known as sunitinib which halts the progress of metastatic kidney cancer. Sunitinib

is one of the few pharmaceutical drugs that provide clear improvements in this type of cancer. The mechanism of functioning of sunitinib is blocking the generation of new blood vessels. Tumors, in order to grow, need to develop blood vessels. Sunitinib impedes their growth, blocking a factor known as VEGF, and other similar ones, which stimulate vascular growth. In phase III of the research, sunitinib was compared with interferon (a type of immunotherapy) in 750 patients with metastatic kidney cancer. It was shown that sunitinib is more efficient in halting the progress of the disease. Over 101 medical centers from all over the world took part in this research. The treatment is well tolerated though certain side effects can occur, such as hypothyroidism, high blood pressure and fatigue, which have to be taken into consideration. The use of sunitinib in Spain is to be approved shortly for the treatment of kidney cancer with metastasis.

*(Science Daily, Mar 2, 2007)*

### Tykerb – New Targeted Therapy

The Food and Drug Administration (FDA) of USA has approved Tykerb (lapatinib), a new targeted anti-cancer treatment, to be used in combination with capecitabine (Xeloda), another cancer drug, for patients with advanced, metastatic breast cancer that is HER 2 positive (tumors that exhibit HER 2 protein). The combination treatment is indicated for women who have received prior therapy with other cancer drugs, including an anthracycline, a taxane, and trastuzumab (Herceptin).

Tykerb, a new molecular entity, is a kinase inhibitor working through multiple pathways to deprive tumor cells of signals needed to grow. It is a small molecule that enters the cell and blocks the function of HER 2 protein and other proteins. Trastuzumab, a monoclonal antibody, is a large protein molecule that targets the part of the HER 2 protein on the outside of the cell. Because of this difference in mechanism of action, Tykerb works in some HER 2 positive breast cancers that have been treated with trastuzumab and are no longer benefiting. Tykerb is available in tablets of 250 mg. An undivided dose of 1250 mg should be taken orally once daily for 21 days in combination with capecitabine on days 1-14 of a 21-day cycle.

*(FDA News, Mar 13, 2007)*



## LUNG CANCER

### Navigation Guided Bronchoscopy

For small peripheral lung lesions in the patients considered unsuitable for straight forward surgery or CT guided transthoracic needle aspiration biopsy due to comorbidities, a navigation study was facilitated by an electromagnetic tracking system which could detect a position sensor incorporated into a flexible catheter advanced through bronchoscope. Information obtained during bronchoscopy was superimposed on previously acquired CT data. Divergence between CT data and data obtained during bronchoscopy was calculated by system's software. All target lesions but one was reached and the overall diagnostic yield was 62.5% (25/40). Diagnostic yield was significantly affected by CT-to-body divergence; yield was 77.2% when estimated divergence was  $\leq 4$ mm.

According to this study, electromagnetic navigation guided bronchoscopy has the potential to improve the diagnostic yield of transbronchial biopsies without additional fluoroscopic guidance and may be useful in early diagnosis of lung cancer, particularly in non-operable patients.

*(Eur. Respir J, Mar 14, 2007)*

### PET-CT for Solitary Pulmonary Nodules

Oriacchio A et al from Italy evaluated fifty-six indeterminate solitary pulmonary nodules (SPNs) using an integration of [(18F)-2-fluoro-2-deoxy-D-glucose positron emission tomography [(18F)-FDG-PET with contrast-enhanced Multi Detector Computed Tomography (MDCT). The results indicate that PET/CT allows accurate analysis of anatomical/morphological and metabolic/functional correlations of SPN, providing useful data for identifying and locating the disease, for differentiating between malignant and benign nodules and for establishing the aggressiveness and degree of vascularity of pulmonary lesions. In view of the considerable reduction in time and cost of the single examinations, the authors believe that PET/CT would gain an increasingly dominant role in the diagnostic and therapeutic approach to lung cancer.

*(Radiol Med (Torino), Mar 19, 2007)*

### Pulmonary Radiofrequency Ablation

A study by the Brown Medical School and Rhode Island Hospital showed that radio frequency (RF) ablation used to treat early stage, inoperable lung cancer resulted in outcomes that were equal to or better than those achieved through External Beam Radiotherapy (EBRT), a decades old alternative to the surgical removal of cancerous tissue. Conventional EBRT involves 33 treatments over a six-week period and can often lead to side effects. RF ablation, which uses high frequency electric currents to heat and destroy abnormal cells, is performed in a single day as an outpatient procedure, is minimally invasive and has few side effects.

The study showed that RF ablation produced meaningful results in terms of both survival and tumor control. The best two-year survival rate for early-stage lung cancer using EBRT was 51 percent, compared to 57 percent with ablation. RF ablation helped control the progression of patients' tumors. Tumors 3 cms or smaller took an average of 45 months to grow following treatment; tumors larger than 3 cms progressed in an average of 12 months. As the means of detecting early stage lung cancer improves, less invasive treatment options such as ablation replacing surgery would be seen in future.

*(Radiological Soc. of N. Amer, Mar 28, 2007)*

### Radiation Preferred Over Surgery

According to a randomized controlled trial, after an initial chemotherapy treatment, radiation may be a better choice than surgery for patients with stage 111A non-small-cell lung cancer (NSCLC). Approximately 80% of all lung cancers are NSCLC and of those patients diagnosed with NSCLC, about 30% have locally advanced stages 111A or 111B. Under this trial the patients were first given three cycles of platinum based chemotherapy of those who responded to the treatment, 61% of the initial group were then randomly assigned to receive either surgery or radiation. The researchers found that surgery, compared to radiation, did not improve survival after treatment with chemotherapy. The authors concluded that radiation was the preferred treatment because of its lower rate of complications and mortality in lung cancer patients.

*(J of Nat Cancer Inst., Mar 22, 2007)*

## LEUKEMIA

### Diagnosis of CLL

According to updated guidelines from the National Comprehensive Cancer Network (NCCN) for diagnosis of Chronic Lymphocytic Leukemia (CLL), bone marrow biopsy is less important than molecular and cytogenetic evaluation. Instead of bone marrow as a predictor, the panel is looking at FISH (Fluorescence In Situ Hybridization) status and IgVH mutational status. The panel felt that bone marrow biopsy was not essential for the diagnosis of CLL. "Traditional" high risk parameters included Rai stage, lymphocyte doubling time, Beta2 microglobulin and pattern of marrow involvement, "modern" risk parameters incorporate mutational status for the Zap-70 (Zeta-chain-associated protein 70 KD) protein and CD 38 glycoprotein along with FISH status. Regarding assessing mutation status, although commercially available, in-house availability is possible in large academic centres. Guideline panel members noted that the correlation of CD 38 with mutation status remains under debate and expression of ZAP 70 needs to be carefully calibrated.

*(Doctor's Guide, Mar 21, 2007)*

### Early Infection Tied to Leukemia

The chances of children being diagnosed with leukemia seem to be related to the number of infections they had in their first year of life, according to a research from UK. The findings support the theory that "a dysregulated immune response to infection in the first few months of life" promotes the development of Acute Lymphoblastic Leukemia (ALL) later in childhood. According to the research, children diagnosed with most common leukemia ALL had significantly more infectious episodes in infancy than did a comparison group of matched "controls" without leukemia. Children with ALL who had more than one neonatal infectious episode tended to be diagnosed with ALL at a comparatively young age. The average age when ALL was diagnosed was 38 months for children with two or more episodes of infection in the new born period, compared to 45 months for kids with only one episode or none. The research showed that early infection is positively associated with early onset ALL.

*(Reuters Health, Mar 12, 2007)*

### Risk of Secondary Cancers

Acute lymphoblastic leukemia (ALL) is the most common and curable pediatric cancer. Most of the survivors are cured with no evidence of disease for at least 10 years. The study conducted by the researchers at St. Jude Children's Research Hospital showed that survivors of ALL have a significantly increased risk of secondary neoplasms developing over 30 years after leukemia treatment when compared to the general population. Secondary neoplasms are new tumors that develop after successful treatment of an initial cancer. The study found that most of these late-onset secondary neoplasms are low-grade, or slow-growing, tumors that are curable, specifically meningiomas and basal cell carcinomas. However, a substantial number were more aggressive tumors such as soft tissue sarcomas and carcinomas. Even though they are low grade and curable, they may cause significant health issues, so medical care should not end when the survivors go home. To lower the risk of second cancer in the future, some institutions omit the use of radiation in the treatment of leukemia patients.

*(American Medical Association, Mar 21, 2007)*

### Treatment of Mixed Lineage Leukemia

The paper published by Ali Shilatifard, under the title "The trithorax group gene little imaginal discs in drosophila encodes a histone H3 trimethyl - Lys4 demethylase" identifies a cellular factor that can reverse histone trimethylation associated with mixed lineage leukemia (MLL). This will allow the identification of new targets for the treatment of leukemia caused by MLL translocations (histone H3K4 methyltransferase).

Little imaginal disc (Lid) removes methyl groups from histone H3K 4. A reduction of Lid results in a specific genome wide increase in H3K4 trimethylation levels with no effect on other patterns of histone trimethylations. Animals with reduced Lid levels have higher level of H3K4 trimethylation resulting in altered distribution of the chromo-helicase protein, the CHD1. The role of MLL in a variety of blood related cancers has been well established. These findings give a promising option for developing targeted treatments to combat these types of leukemias.

*(Science Daily, Mar 14, 2007)*

## CANCER CONTROL

### A Way to Slow Prostate Cancer

A component of green tea combined with a low dose of COX-2 inhibitor may act in concert to slow the spread of human prostate cancer. In the current study by Mukhtar's team at the University of Wisconsin, Madison, treatment of cultured human prostate cancer cells with a COX-2 inhibitor, celecoxib or green tea extract, polyphenol, significantly inhibited prostate cancer cell growth, but the combination was most effective, increasing cancer inhibition 15% to 28% more than the additive effects of the two therapies alone. Celecoxib and green tea have a synergistic effect, each triggering cellular pathways, that when combined are more powerful than either agent alone. This is the first time a synergism between these agents against prostate cancer cells has been demonstrated. If tests in human trials replicate these results, we could see a powerful combination therapy that is both simple to administer and relatively cost effective.

*(Biocompare, Mar 15, 2007)*

### Cancer-Fighting Foods & Supplements

Researchers worldwide are discovering a cornucopia of compounds in food and dietary supplements that show promise for preventing cancer. Researchers at Ohio State University showed that diet supplemented with black raspberries had a 60% reduction in tumors of the esophagus and up to an 80% reduction in colon tumors in animal models. Clinical trials are now underway in humans.

A compound, petrostilbene, a potent antioxidant found in blueberries shows promise of preventing colon cancer. Chemicals obtained from grape seed extract show promise to prevent sunlight induced skin cancer when used as a dietary supplement. Grape seed compounds, a group of antioxidants called proanthocyanidins inhibit suppression of the immune system caused by ultraviolet light exposure. A dietary component found in most whole grain foods, beans, nuts and other high fibre items is a potent weapon for preventing prostate cancer. The compound, inositol hexaphosphate (IP6) sold in stores as a dietary supplement, adds to the growing number of products including lycopene, milk thistle extract, vitamin E and selenium that also have shown promise against prostate cancer. Drinking two to three glasses of cloudy apple

juice (unfiltered) per day may help keep colon cancer at bay due to a potent class of antioxidants called procyanidins. Cloudy apple juice is richer in oxidants up to four times than clear apple juice.

*(American Chemical Society, Mar 26, 2007)*

### Colonoscopic Surveillance

According to researchers, colorectal cancer patients should undergo routine colonoscopic surveillance at one year after their surgery and that more intensive surveillance may be needed in patients found to have advanced neoplasia as well as those with a prior history of adenomatous colon polyps. Colorectal cancer survivors benefit from surveillance with colonoscopy and it appears that the initial surveillance should be performed at one year after colon resection because of the significant risk of additional cancers and polyps in these patients. Study by Stephen J. Rulyak et al showed that patients who underwent one or more colon examinations during follow up had improved survival compared with patients who did not undergo examination. Patients with a prior history of adenomas were more likely to have advanced neoplastic polyps on follow up. Patients with advanced neoplastic polyps on the initial surveillance colonoscopy were frequently found to have advanced neoplasia on subsequent colonoscopies. 3.1% patients in the study group were diagnosed with second colorectal cancer. This study provides proof of the value of screening and the lives that can be extended and saved.

*(Medical News Today, Mar 18, 2007)*

### Lymphedema Prevention

Surgery to remove the lymph nodes and most of the fat and tissue in the armpit often resulted in arm swelling called lymphedema. To prevent the arm swelling in breast cancer patients, Klimberg of the University of Arkansas for Medical Sciences (UAMS) has developed a new procedure called Axillary Reverse Mapping (ARM) procedure. The new technique evaluates the ways in which fluid drains through the lymph node system in the arm through the injection of blue dye. The dye is used to map the drainage of the arm. This decreases the chances of unintended disruption of the lymph node system during surgery and reduces the risk of developing swelling in the arm. Klimberg said that they were the first to study lymph node drainage in the arm and to now use the ARM procedure as standard procedure at UAMS.

*(UAMS, Mar 17, 2007)*



## INSTITUTION

### INSTITUTE OF CYTOLOGY AND PREVENTIVE ONCOLOGY

#### Introduction

Institute of Cytology and Preventive Oncology (ICPO) was initially established as Cytology Research Centre (CRC) in 1979 by the Indian Council of Medical Research (ICMR). ICPO came into existence in 1989 when CRC was elevated to the level of an Institute. In the year 2006, ICPO moved from Maulana Azad Medical College Campus, New Delhi, to its new sprawling campus at Sector 39, Noida.

ICPO was instituted with the main aim of promoting basic biological and clinico-epidemiological research in the field of cancers that are most prevalent in India with an emphasis on their early detection, primary and secondary prevention. The Institute carries out multidisciplinary studies to understand the natural history, biological behaviour and mechanism of human carcinogenesis. It has developed well defined thrust areas for cancer research since its inception. It is translating research leads from laboratories to the field through operational research. ICPO has built up a unique approach by amalgamating very strong basic, clinical and applied research, involving both clinical and basic scientists.

#### Research Divisions

The major research divisions of ICPO include Clinical Oncology, Cytopathology, Molecular Genetics and Biochemistry, Molecular Oncology, Immunology and Virology, Epidemiology and Biostatistics, Behavioral Oncology, Bioinformatics and Drug Designing, Vaccinology, Cellular and Molecular Diagnostics, Human Resource Development, and early detection and referral services.

#### Thrust Areas of Research

High quality research work in the fields of cervical cancer, breast cancer, tobacco related cancers, oral cancer, esophageal cancer, lung cancer, ovarian cancer, gall bladder cancer, liver cancer, prostate cancer and other cancers are currently being undertaken at ICPO.

#### Major Research Programmes

**Cervical Cancer:** The Institute carries out early detection, including visual inspection and development of alternative strategies, management of cervical precancerous lesions using cytomorphological and clinical approaches, molecular markers for the detection and progression of cervical cancer, role of genetic polymorphism of GSTM1 and GSTT1, HLA and cytokine genes. The HPV programmes of ICPO include biological behaviour of HPV infection, development of low-cost diagnostic tests, development of HPV-DNA diagnostics for early detection of cervical cancer, transcriptional control of HPV infection, development of anti-HPV therapeutics, development of HPV-DNA vaccine and clinical evaluation of existing HPV sub-unit vaccine.

**Breast Cancer:** Under this programme, studies are being carried out on screening of breast lumps by medical and paramedical staff, multidisciplinary study on breast cancer to determine risk factors, genetic susceptibility, gene mutations, prognostic factors including hormone receptors, BRCA1 and BRCA2, p53 gene mutation, methylation, expression and transcription regulation.

**Other Cancers:** Research programmes on other cancers include role of tobacco and pesticides in oral, esophageal, stomach and lung cancers in northeast region of India, molecular epidemiology, gene expression profiling, role of transcription factors, NF- $\kappa$ B and AP-1 in oral cancers, molecular investigators of ovarian and liver cancers.

#### Highlights of Achievements

1. Established for the first time that HPV prevalence in cervical cancer is the highest (98%) and HPV 16 is the type exclusively high (~90%) in India.
2. A 12-year follow-up study of 1100 dysplasia cases along with controls demonstrated that more than 70% of those progressed to carcinoma were positive for high risk HPV types 16/18.
3. Women with high risk HPV and consummation of marriage under 18 years increased the risk of cervical cancer by 22 fold.
4. Higher the number of pregnancies greater the chances of HPV infection and cervical cancer.
5. Use of urine for the detection of HPV infection in the uterine cervix opened up a novel approach for a non-invasive screening of women who are likely to progress to cancer.
6. Discovery of simple paper smear method of dry collection, transport and storage of cervical specimens

for cost-effective mass screening of HPV for early detection of cervical cancer. Patent application for this technique under US patent application No. 10/444, 988 has been filed. It is being commercialized with the help of industry.

7. Developed cost-effective molecular methods for screening and typing "high risk" HPVs.
8. Institute is speeding up the microarray based gene expression profiling for the development of clinically valid and commercially viable customized gene array for early detection of cervical cancer and also the possibility of identifying the patients at risk of aggressive disease.
9. A novel tumor suppressor gene site (D5S406 locus) on chromosome #5 has been identified in precancerous and cancerous lesions of uterine cervix. This can be used as a biomarker for identifying the high-risk population for developing precancerous lesions.
10. Institute has initiated its vaccine program in collaboration with WHO, Geneva; Department of Biotechnology, India, and private industries to develop vaccine against Human Papillomavirus to control cervical cancer.
11. Novel mutation in BRCA1 gene has been discovered in familial breast cancer patients in India.
12. Institute has developed simple magnified visual device with light source for an easy inspection of cervix in the field, Magnivisualizer, and has applied for Indian patent. (Application No. 320/del/2000).
13. Curcumin, the active ingredient of turmeric is shown to be a potent inhibitor of HPV/cervical cancer – a possible potential anti-cancer herbal drug. This is under multicentric clinical trial with DBT funding.
14. Cancer detection camp and public awareness programme regarding the risk factors related to development of cervical precancer and cancer such as at early age consummation of marriage, sexual promiscuity, smoking habits and unhygienic genital practices were carried out through exhibitions and audiovisual approaches.
15. Human resource development through workshops, in-service training, MD, MS, DNB and DM and PhD programmes, MSc dissertation projects and summer training in the fields of Molecular Biology, Immunology, Pathology, Clinical Cancer Research and Molecular Medicine.
16. Diagnostic Referral Services for cancer cases from as many as 13 government hospitals.

17. Training manpower for early detection of cervical cancer through visual inspection.

### New Initiatives

1. DBT multicentric clinical trial study has been undertaken to investigate the clearance of HPV infection in uterine cervix by BASANT, a polyhedral vaginal cream and curcumin. Curcumin is a potent anti-HPV molecule and is under patenting.
2. Comparative study of genetic, clinical and epidemiological factors of breast cancer in rural and urban areas of India is being formulated.
3. Development of prophylactic DNA based genetic vaccine against HPV.
4. Assessment of prevalence of tobacco use and impact of health education intervention among school students is being pursued.
5. Development of regional HPV laboratory for monitoring HPV vaccine programme under WHO's initiative for development of a global HPV laboratory network for HPV vaccine monitoring.
6. Development of Centre of Excellence in papillomaviruses.
7. Understanding of molecular mechanisms of HPV mediated carcinogenesis through micro-array and protein array technology.
8. Development of clinics and clinical networking with local and general cancer hospitals of National Capital Region for establishing cancer screening diagnostic and referral facilities.
9. Development of proteomics laboratory.
10. In order to develop human resources in the field, School of Cytology, Diploma Course in Cellular and Molecular Oncology for Medical Postgraduates (duration 1 year/6 month), Training in Gynae Cytology Clinical Examination, Colposcopy Training for Medical Postgraduate Students, Management of Precancerous Lesions, School of Behavioural Oncology have been initiated.

### Conclusion

ICPO has developed specialized manpower in the field of oncology and is thus today the National Referral Centre for Human Papillomavirus, WHO Collaborating Centre for Research and Training in Cytology, Member-International Union against Cancer (UICC), and WHO Collaborating Centre for Global HPV and Vaccine Programme.

## CLINICAL TRIALS

### Combined Adjuvant Therapy

Some early-stage breast cancers are effectively treated with surgery and radiation therapy alone, while others (particularly those that have spread to nearby lymph nodes) also require systemic treatments, such as chemotherapy, hormonal therapy or targeted therapy. Researchers with the Adjuvant Breast Cancer (ABC) trials group conducted two phase III clinical trials to evaluate whether combinations of different types of adjuvant therapy are more effective than single modality therapy. Results showed that the addition of chemotherapy to tamoxifen for the adjuvant treatment of early breast cancer produces modest but sustained improvements in overall survival. The second phase III trial, did not find an overall benefit of adding ovarian suppression to treatment with tamoxifen among premenopausal breast cancer patients. The benefits of each of the treatments evaluated are likely to vary by estrogen receptor status. Women diagnosed with early breast cancer may talk to their physicians about specific characteristics of their cancer and optimal approach to adjuvant hormonal therapy, chemotherapy and/or targeted therapy.

*(UFSCC, Apr 9, 2007)*

### Gleevec Prevents Cancer Recurrence

Preliminary results from a large, randomized, placebo controlled breakthrough clinical trial for patients with primary gastrointestinal stromal tumor (GIST) showed that patients who received imatinib mesylate (Gleevec) after complete removal of their tumor were significantly less likely to have a recurrence of their cancer compared to those who did not receive Gleevec. The standard treatment for primary GIST is complete surgical removal of the tumor without additional therapy. Conventional chemotherapy agents have been notoriously ineffective in GIST. Researchers in the multisite study found that approximately 97 percent of patients who received Gleevec (well tolerated by most patients in the study) one year after surgery were alive without a recurrence of their cancer compared to approximately 83 percent who received one year of a placebo. This study for the first time demonstrated that targeted molecular therapy reduces the rate of recurrence after complete removal of a primary GIST.

*(NIH News, Apr 15, 2007)*

### Phase III Trial for Germ Cell Tumor

A team of researchers in Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, USA investigated the role of high-dose chemotherapy (HDCT) as first line treatment in patients with metastatic germ cell tumor (GCT) and poor prognostic clinical features. In the randomized phase III trial, untreated patients with intermediate or poor risk GCT received either 4 cycles of standard bleomycin, etoposide and cisplatin (BEP) alone or 2 cycles of BEP followed with 2 cycles of HDCT containing carboplatin and then by hematopoietic stem cell rescue (BEP + HDCT). The study correlated serum tumor markers alpha fetoprotein and human chorionic gonadotrophin with treatment outcomes as a secondary end point. The routine inclusion of HDCT in first line treatment for GCT patients with metastases and poor predicted outcome to chemotherapy did not improve treatment outcome. Frequent serum marker determinations to estimate marker decline during the first two cycles of BEP chemotherapy provide a clinically useful estimate of outcome.

*(J Clin Oncol., Jan 20, 2007)*

### Uterine Carcinosarcoma

A study was conducted by researchers at the Gynecologic Oncology Group (GOG), on women with a rare, aggressive form of uterine carcinosarcoma. The women who were treated with the drugs ifosfamide and paclitaxel lived a median of five months longer than women who were treated with ifosfamide alone. An unusual feature of uterine carcinosarcoma is that they contain a mix of two types of cancer cells. This phase III study involved 179 women with mixed tumors that had recurred or spread beyond the uterus. Most of the patients had surgery and some had also received radiotherapy but none had previous chemotherapy. Women treated with ifosfamide plus paclitaxel survived for median 13.5 months compared with 8.4 months for those treated with ifosfamide alone. Tumors either disappeared or shrank by at least half in 45% of the patients treated with the combination regimen, compared with 29% of those treated with ifosfamide alone. Progression of disease was delayed for a median of 5.8 months in the combination therapy group, compared with 3.6 months in the ifosfamide only group. Although combination regimen prolonged patient's lives, it did not cure the disease. Researchers agree that better drugs are needed to treat this disease.

*(NCI Clinical Trials, Feb 10, 2007)*



## WATCH-OUT

### Biomarkers in Cancer

Bacus Sarah S (US) et al have been awarded a patent (No. US 2007059785) entitled 'Biomarkers in Cancer', published on March 15, 2007 and filed by Smithkline Beecham Corp (US). The present invention relates to the use of biomarkers in the treatment of cancer and as an aid in clinical decision making regarding which anti-cancer therapy to use in a particular patient. The erb B family of type 1 receptor tyrosine kinases includes erb B1, also known as the epidermal growth factor receptor (EGFR or HER1), erb B2 (also known as Her 2), erb B3 and erb B4. These receptor tyrosine kinases are widely expressed in epithelial, mesenchymal and neuronal tissues where they play a role in regulating cell proliferation, survival and differentiation. Described under this patent are methods of assessing whether a subject with a solid tumor is suitable for treatment with a dual EGFR/erb B2 tyrosine kinase inhibitors, by assessing the relative localization of IERK or PAKT in tumor cells, and/or assessing pre-treatment tumor cell levels of Erb B2.

*(European Patent Office, Mar 24, 2007)*

### Breakthrough Anticancer Drug

Lpath Inc, the category leader in therapeutic agents against bioactive lipids, announced on February 12, 2007 the issuance of US patent No. 7, 169, 390, entitled "Compositions and Methods for the Treatment and Prevention of Cancer, Angiogenesis and Inflammation". The patent broadly relates to methods of treating cancer using sphingomab, Lpath's breakthrough anti-cancer drug candidate. The patent helps to secure Lpath's proprietary position with regard to sphingomab and other sphingosine-1-phosphate (S1P) - binding agents for the treatment of cancer. It represents a major milestone in the company's efforts to develop this powerful drug candidate for the treatment of cancer and other serious diseases. Sphingomab is a monoclonal antibody against S1P, an important bioactive lipid that has been well validated as a cancer drug target. Sphingomab has recently been "humanized" and is in preclinical development. It is expected to be approved by the US Food and Drug Administration for a phase 1 human

clinical trial by the end of 2007. Lpath believes sphingomab may represent the next generation of anti-angiogenesis-based therapeutics.

*(Biocompare, Feb 12, 2007)*

### Inhibition of Cancer Development

Floyd Robert A et al have been granted an Australian patent (No. AU7853658), entitled 'Butylnitronone Containing Compositions for Inhibition of Cancer Development', on March 24, 2007. The invention uses PBN (alpha-phenyl-tert-butyl nitronone) and its derivatives nitronone-based free radical traps which significantly reduce preneoplastic nodule development as well as inhibit hepatocellular carcinoma (HCC) formation at very low levels. Administering PBN in the drinking water inhibits HCC formation. Preneoplastic nodule growth in the liver is significantly suppressed by administering PBN, or some of its natural metabolites in the diet. The effectiveness of PBN in preventing HCC development in the choline deficiency liver model is considered due to its prevention of tumor development after the target cells have already been initiated, i.e. genetically changed into tumor cells.

*(Espacenet.com, Mar 24, 2007)*

### Novel Method to Make Nanoparticles

Nano Med Pharmaceuticals, Inc, dedicated to developing improved therapeutic and diagnostic products to treat or detect cancer and other serious diseases, announced on Jan 3, 2007 that its founders Russell J. Mumper et al have been issued US patent (No. 7,153,525) entitled "Micro-emulsions as Precursors to Solid Nanoparticles". The invention covers processes and applications of nanotemplate engineering, a nanoparticle manufacturing technology used to formulate small molecules, peptides, proteins, plasmid DNA and diagnostic agents. The nanoparticles take minutes, and can involve simply mixing all of the ingredients and the drug in a single vessel. These nanoparticles, when manufactured to contain anticancer drugs, can deliver the drug more effectively to cancer cells that have developed resistance to the drug when administered alone. Based on these data, Nano Med is developing lead product which overcomes multidrug resistance in remission induction therapy in elderly Acute Myelogenous Leukemia (AML) patients. This product is in preclinical development. Safety and efficacy tests are expected to begin in early 2008.

*(Nano Med Pharmaceuticals (R), Inc., Jan 3, 2007)*

## GLOBE SCAN

### Telomerase Identification

Research into cancer, anticancer treatments and aging has advanced through the identification of the composition of human telomerase, an enzyme integral to 85% of all cancers. Cancer researchers around the world have studied the actual protein composition of telomerase, believing it contains any mixture of 32 proteins. A study by Scott Cohen et al supported by the Cancer Council NSW and the National Health and Medical Research Council Australia, reveals that telomerase contains just 2 proteins. No one had been able to purify telomerase because within each cell it's a very rare enzyme. The identification 'switches on a light' for basic cell biology and cancer research. This discovery would speed up the process of delivering successful treatments. Dr. Cohen developed a brilliant new purification technique that made the telomerase identification possible and would be a step towards development of anti-telomerase drugs. These findings would enhance further study of telomerase and identification of new anti-telomerase drugs.

(Australia - *Child' Med. Res. Inst.*, Mar 30, 2007)

### Virus Induced Lymphoma

Researchers at the University of Helsinki have discovered that activation of the p53 pathway offers a novel and effective treatment modality for Kaposi's Sarcoma Herpes Virus (KSHV)-infected Primary Effusion Lymphoma (PEL). PEL patients have survival shorter than six months after diagnosis and there are no current therapies effective against the aggressive KSHV-induced PEL.

The recently discovered strategy for p53 activation targets the interaction of p53 with its negative regulator MDM2. This is based on small molecule inhibitor of p53-MDM2 interaction, the Nutlin-3a. Majority of the PELs appear to have an intact TP53 gene encoding p53. The results of the study show binding of the KSHV latency associated antigen LANA to both p53 and MDM2 and that the MDM2 inhibitor Nutlin-3a disrupts the p53-MDM2-LANA complex and selectively induces massive apoptosis in PEL cells. The cytotoxic effect of Nutlin-3a was specific for the KSHV-infected cells.

(Finland - *University of Helsinki*, Mar 15, 2007)

### Cancer Risk Linked to Alcohol

Ethanol in alcoholic beverages is classified as "Carcinogenic to human (Group 1)". It causes cancers of the oral cavity, pharynx, larynx, oesophagus and liver. The addition of breast cancer and colorectal cancer, two of the most common cancers worldwide, to this list indicates that the burden of cancer attributable to alcohol consumption is higher than previously thought, according to a press release of the International Agency for Research on Cancer (IARC), the cancer research agency of the World Health Organization.

Alcohol is one of the top 10 risks for health. Its consumption is highest in Europe and is increasing in Asia. Relative risk increase for consumption of 50g/day for cancers of oral cavity, pharynx, larynx and oesophagus is two to three-fold compared with the risk in non drinkers. For liver cancer it is difficult to quantify. For breast cancer it is 1.5 compared to that in non drinkers and for colorectal cancer, it is 1.4. The adverse effects of alcohol and smoking seem to be multiplicative. Public health action against alcohol consumption, especially excessive alcohol consumption, needs to be stepped up to reduce global cancer burden.

(France - *IARC Press Release*, Mar 28, 2007)

### Ovarian Cancer Biomarkers

The team of researchers from the University of Pennsylvania, the University of Michigan and universities in Greece and Italy, have identified markers unique to the cells of blood vessels running through ovarian tumors. The findings, while preliminary, could one day improve screening, diagnosis, treatment and prognosis for this disease. They used a laser technique to isolate blood vessel cells from 21 ovarian tumors and four normal ovarian tissue samples. From there, they were able to determine which genes the vascular cells expressed. They identified more than 70 markers in the blood vessels of cancer tissue but not in the normal tissue. Some of the genes were highly expressed. It may be a sign of a tumor that's able to grow blood vessels more efficiently and therefore is more aggressive. This may help us down the road in treatment decisions. They found that markers are specific to tumors. If the markers do prove to be specific to ovarian tumors, it could be a new avenue to develop drugs that would target the blood vessels and strangle the tumor.

(USA - *Biocompare*, Mar 7, 2007)

## CERVICAL CANCER CURRENT AND FUTURE DIRECTIONS

**RGCON – 2007**, the 6<sup>th</sup> International Conference was organized by Rajiv Gandhi Cancer Institute and Research Centre, Delhi, on 31<sup>st</sup> March and 1<sup>st</sup> April 2007. The theme of the conference was “**Cervical Cancer – Current Management and Future Directions**”. It was inaugurated by Mrs Sheila Dikshit, Honorable Chief Minister, Govt of NCT, Delhi. Dr T. Ramasami, Secretary, Department of Science and Technology, and Prof V.S. Ramamurthy, DAE, Homi Bhabha Chair Professor, were guests of honour at the inaugural function.

In India an estimated 0.8 to 1 million new cancer patients are detected each year. Carcinoma of the cervix constitutes 20 to 25% of all cancers seen among females. 1.2 to 1.3 lac cases of carcinoma cervix are diagnosed annually in India. Globally, breast cancer is the leading cancer in women followed by cancer of the cervix. Incidence rates of cervical cancer are two-fold higher in less developed countries than in more developed countries – 19.1 vs 10.3 per 100,000 py.

Despite many predisposing factors, exact etiology of cervical cancer is not known. Certain associated factors include low socio-economic status, smoking, low intake of vitamins and micronutrients, multiple sexual partners, sexual relations at young age, oral contraceptives and Human Papilloma Virus (HPV). HPV subtypes 16 and 18 have been established as the sexually transmitted virus responsible for initiating carcinoma cervix in more than 90% of the cases in the developing countries such as India.

Over 300 delegates from India, neighbouring countries like Nepal and China, Thailand and Malaysia, and Europe (Austria and UK), and Canada attended the conference. Esteemed faculty from USA, Canada and Europe and India provided expertise in scientific sessions. The conference was attended by renowned national and international speakers from Surgical Oncology, Radiation Oncology, Medical Oncology, Pathology and Medical Physics to make it a focussed conference on Carcinoma Cervix with high scientific content.

On the first day of the conference, the Harish Chandra Bajoria Memorial Oration was delivered by Dr. K.A. Dinshaw, Director, Tata Memorial Hospital (TMH), Mumbai. She spoke on “The Perspective, the Reality and the Promise – Cancer Cervix: Year 1979 – 2006”. Dr Raman Chadha Memorial Oration was

delivered by Dr Uma Devi, Head, Dept of Gynaecologic Oncology, Kidwai Memorial Institute of Oncology, Bangalore, on the second day of the conference; it covered the important topic of “Management of Pre-invasive Carcinoma Cervix”. She covered most of the aspects related with prevention, screening and early detection of cervical cancer so important for women of developing countries like India.

The conference started with the morning session on “Molecular markers and techniques in early detection of carcinoma cervix”. Dr Maqsood Siddiqi's (Cancer Foundation of India, Kolkata) paper “Issues on early detection of carcinoma cervix” was read by Dr A. Rajwanshi from PGI, Chandigarh and the status of HPV vaccine was highlighted by Dr Neerja Batla from AIIMS, New Delhi.

Newer developments in investigative workup were covered in a symposium. Panelists included Dr G.P. Vashisht from Batra Hospital, New Delhi, Dr V. Kannan from P.D. Hinduja Hospital, Mumbai, Dr Supreeta Arya from TMH, Mumbai, Dr V. Rangarajan from TMH, Mumbai and Dr Richard Potter from University of Vienna, Vienna. Various aspects of CT scan, MRI and CT-PET related to diagnostic workup of carcinoma cervix were discussed in detail.

Dr K.A. Dinshaw of TMH advised colposcopy and pap smear for cervical cancers as effective screening measures. She also discussed the use of HPV vaccines as an effective alternative strategy to screening programmes for reducing the burden of cervical cancer in India and other developing countries. Acquisition of newer diagnostic and treatment facilities, evaluation of patients at joint clinics with refinement in treatment protocol and following established clinical guidelines, and successful screening strategies, have made a significant impact in the cervical carcinoma survival outcomes.

Dr Robert Pearcey from Cross Cancer Institute, Edmonton, Canada, discussed the adoption of policy of using radiation and chemotherapy together in locally advanced cervical cancer patients. Through translational research, this policy has become the standard of care in most of the institutes globally and has led to the improvement in local control and survival. Newer chemotherapy drugs and biological agents are also being tried and they also have promise. However, concurrent chemoradiation is associated with higher risk of side effects for which more refined ways of delivering radiation therapy, such as Intensity





Smt. Sheila Dikshit, Chief Minister, Govt. of NCT, Delhi with Guests of Honour Dr T. Ramasami, Secretary and Prof V.S. Ramamurthy, Ex-Secretary, Department of Science and Technology and members of Organizing Committee at the inaugural function.

Modulated Radiation Therapy (IMRT), are increasingly being adopted in clinical practice.

Dr G. Kilara, Director, Curie Centre of Oncology, Bangalore, discussed the treatment options for patients who are diagnosed with early stage of cervical cancer. Surgery and radiation therapy have almost similar control rates. In young patients with very early stage of the disease, newer techniques of surgery like laproscopic lymphadenectomy and vaginal trachelectomy have been suggested to preserve the fertility.

Dr. H.B. Tongaonkar, Prof and Head of Uro Gynae Oncology, TMH, Mumbai, deliberated on indications and techniques of surgical management of early stage of carcinoma cervix. Dr Aruna N Kekre, Department of Obstetric and Gynae, Christian Medical College & Hospital, Vellore, highlighted some of the aspects related to complications of surgery and the impact of newer surgical techniques.

Dr G.K. Rath, Head, Department of Radiation Oncology, IRCH, AIIMS, New Delhi, presented a compilation of pattern of care studies regarding the management of carcinoma cervix since 1972. Over the last 35 years, several of these studies have been undertaken and have contributed to the knowledge related to different aspects of treatment of carcinoma cervix.

Dr V. Kannan, Consultant & Head, P.D. Hinduja Hospital, Mumbai, discussed about the latest techniques of radiation therapy like 3D-Conformal radiation and Intensity Modulated Radiation Therapy in the treatment of carcinoma cervix. These sophisticated techniques deliver very precise radiation to the tumor while sparing surrounding normal organs like urinary bladder, rectum and small intestines. Many institutes all over the world have adopted this technique to improve the outcome of this cancer.

Dr Richard Potter, Professor at University of Vienna, Vienna spoke about brachytherapy which has been used world-wide over the last decades. Significant improvements have been achieved recently with the introduction of sectional imaging like CT-scan and MRI scan. Introduction of CT-PET scan has added another dimension by identifying the portion of the tumor which has actively multiplying tumor. It has led to the development of "Image based brachytherapy" where specified dose of radiation can be delivered to more precisely identified area of disease extension with the help of MRI and CT-PET scan. It has reduced the dose to the surrounding normal organs like bladder, rectum, sigma and small bowel leading to reduction in morbidity associated with radiation therapy.

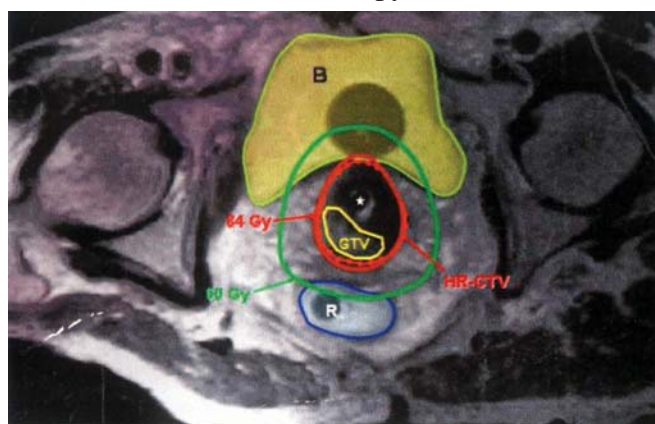


Image Based Brachytherapy with the help of MRI. GTV – Gross Tumor Volume, CTV – Clinical Target Volume

These developments would also help in developing "Intensity Modulated Radiation Therapy" for cervical cancer patients. These entire newer technologies have already started showing result in the form of better control of cervical cancer with simultaneous reduction in treatment related side-effects.

Dr C. Kirisits, University of Vienna, Vienna highlighted the dosimetric advantages of delivering brachytherapy over the last decades under the visualization and guidance of MRI scan. It would deliver radiation exactly at places where disease is seen to be extending on MRI scan. It is a major step in "Image Based Brachytherapy" for cancer of the cervix.

Dr Narendra Pisal from Whittington Hospital, NHS Trust, London, UK and Dr Neerja Batla (AIIMS) conducted the colposcopy workshop covering some of the burning issues related with it.

Thus, the two-day scientific feast covered most of the aspects related with the prevention, screening and early detection of cervical cancer so important for women of developing countries like India.