

UConn Cancer Dialogue

REMARKABLE CARE THROUGH RESEARCH AND EDUCATION



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First Year In Review



l to r: Victor Moyo, MD, Assistant Professor Medicine, UConn Cancer Center; Upendra Hegde, MD, Assistant Professor Medicine, UConn Cancer Center; Pramod Srivastava, Ph.D., Physicians Health Services Chair in Cancer Immunology and Director, UConn Cancer Center

Our beginnings

It has been one full year since the establishment of the University of Connecticut Cancer Center (UCCC). This new program was created to integrate and coordinate the cancer mission across the Schools of Medicine and Dental Medicine, the Graduate School, the John Dempsey Hospital, and other institutional programs including those established via the Research Strategic Plan.

Like most new efforts, the beginning has evoked an inevitable sense of excitement, brought some successes, and a few challenges yet to be realized. Here's a brief account of the beginning:

Recruitments. We had the pleasure of recruiting two fine and well-trained medical oncologists. Dr. Victor Moyo and Dr. Upendra Hegde, trained most recently at Johns Hopkins and at the National Cancer Institute respectively,

joined us this fall. Both have assumed their clinical responsibilities and are treating cancer patients. They are also developing research initiatives to complement the translational research already being conducted at the UCCC. Indeed, integration of new, highly capable scientists and clinicians into the academic mission of the UCCC is a hallmark of our vision and will be pivotal to our future accomplishments.

New clinical trials. Several new vaccine trials for the treatment of patients with chronic myelogenous leukemia (CML) and cancers of the ovaries and cervix have been initiated. The process of implementation of trials of this scope is tedious. I am pleased to report that enrollment of patients is near completion for the CML study and patient recruitment is about to begin for the cervical/HPV (human papilloma virus) study. The ovarian protocol will commence recruitment by January 2003.

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The foundation upon which these trials originate is grounded in the research efforts and scientific discoveries of investigators at UCCC. We await the not-too-distant-day when patients and physicians in our community collectively shall look upon UCCC as a unique resource for "Remarkable Care through Research and Education." Our ultimate goal at the UCCC is that all patients admitted to the Center shall be offered the opportunity to enroll in novel experimental therapies for cancer.

Connecticut Tumor Bank. The State of Connecticut houses the country's oldest tumor registry. We have now added to that distinction by creating at the UCCC the country's first public tumor bank. Initiated partly through the generosity of the UConn Cancer Research Golf Tournament, the program shall be launched January 1, 2003.

It is increasingly clear that every cancer is distinct in its biology. Understanding the molecular uniqueness is the key for designing true individually tailored therapies. Moreover, only cancer tissue based analysis will enable researchers to study normal gene arrangements as well as abnormal changes that may allow a given cancer to develop. To this end, every cancer patient who undergoes a surgical procedure at UCHC will have his/her tumor banked. This human tumor bank will serve as a centralized facility for the acquisition, retention, and release of human tumor to the scientists at the Health Center who are conducting basic and clinical research. This program will centralize the methodology and sample access in order to permit comprehensive analysis such as immunohistochemistry, in situ hybridization, isolation of messenger RNA microarrays, and analysis of chromosomal rearrangements, mutations and DNA modification. Thus,

scientists and clinicians will be able to examine the molecular fingerprint for the patient's tumor. Should some present or future research indicate that a particular characteristic of a patient's tumor makes him/her eligible for an experimental treatment, that information shall be available to the patient and will enable him/her to apply to enroll in that trial at UCCC. In addition, large scale molecular fingerprinting of patients' cancers will lead us into new methods of diagnoses and treatment of cancers. To ensure standardized methods, we have hired a research associate whose role will include maintenance and adherence to stringent regulatory and technical parameters. Patients shall not incur any charge for creation of the molecular fingerprint of their cancers.

Communication with oncology physicians and nurses. Communication with community physicians and their patients remains a crucial component of our plans. Indeed, the Cancer Education Committee was established one year ago to create and maintain a coordinated cancer curriculum for health professionals, the public and the State legislature.

To this end, we have undertaken several new programs including publication of the Dialogue. The Dialogue is intended as a means of communication with oncology health professionals. It emphasizes the central role of translational research within the Cancer Center's mission, and provides educational updates for health professionals involved in the care of cancer patients, as well as research scientists working in the laboratory.

A new monthly curriculum, the UConn Cancer Center Seminar Series, has also been implemented via generous

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New Faculty Speaks to the Future of Cancer Research

S P O T L I G H T

By *Upendra Hegde, MD*
Assistant Professor
Hematology /Oncology
UConn Cancer Center



I elected to join the Cancer Center at UConn at a unique time in the program's evolution. The plan to integrate the basic and translational research components of the academic mission with multi-professional education and patient care is innovative and exciting. My transition this summer from completion of a hematology/oncology fellowship at the National Cancer Institute to full-time faculty status at the Health Center has afforded me the opportunity to reflect on the current status and future directions of molecular medicine and clinical oncology practice.

Recent advances in cancer treatment have come from the tremendous progress in basic research including molecular biology, genetics and immunology. It is becoming increasingly clear that there is a complex molecular basis for multiple mechanisms associated with tumor cell proliferation, differentiation and

cell death. In addition, advances in the protein chemistry/purification techniques have identified new ligands to novel receptors on cell membranes. Together with the molecular biological advances in the laboratory, researchers and clinicians have gained insight into the various signal transduction pathways in a tumor cell as well as various molecules responsible for their regulation. Such discoveries have led us to development of "designer" molecules targeted to blocking such pathways.

Successful development of a receptor tyrosine kinase inhibitor STI-571 represents the proof of this principle that directs the translational research potential. Many important enzymes or proteins are linked to the genes on the chromosomes, mutations of which affect cellular proliferation and differentiation that influences development of cancer. The simultaneous coordinated expression of thousands of genes that participate in the growth of cancer cells can now be systematically studied. This information not only provides relevance of a group of genes but also aids in development of a basic research strategy to test new agents that targets specific molecular pathways of tumor growth. Immunologic advances have provided investigators the ability to develop monoclonal antibodies against tumor proteins. These highly specific monoclonal antibodies can either be administered as individual moieties or be attached to toxins or radioactive isotopes to evoke tumor killing without damage to normal tissues.

The role of a functional immune system in tumor control has resulted

in the development of a variety of new ways to stimulate such a host mediated anti-tumor response based on the targeting of unique tumor proteins. An array of tumor vaccine strategies have been implemented into clinical trials for the treatment of cancer. Encouraging results of such strategies have already been observed in follicular lymphomas and have attracted significant interest in other solid tumors.

A variety of different mechanisms exist in a tumor cell that causes a tumor to clonally expand and metastasize. Thus, a multi-modality approach for therapy may be superior to single agent approaches. Researchers and clinicians representing the basic and clinical sciences are thus collaborating to develop a curative approach to cancer. Such a principle is scientifically sound and has produced dramatic results in our ability to successfully treat more cancers today than in the past.

I firmly share this approach relative to defining novel technologies for the successful management of the cancer. At the Health Center, highly skilled basic and clinical scientists are collaborating intensively in several scientific domains including molecular biology, genetics and immunology. I see an important and elegant opportunity to be able to work with them, identify the targets and develop new treatments to diverse group of tumors utilizing this multidisciplinary approach. My training in Hematology and Oncology at the National Cancer Institute is based on this principle, which I hope will help me achieve my goals of providing state of the art treatments to oncology patients.

UConn Cancer Center Multidisciplinary Head and Neck Program

By **Jeffrey D. Spiro M.D.**
Professor of Surgery
Division of Otolaryngology/Head
and Neck Surgery
UConn School of Medicine

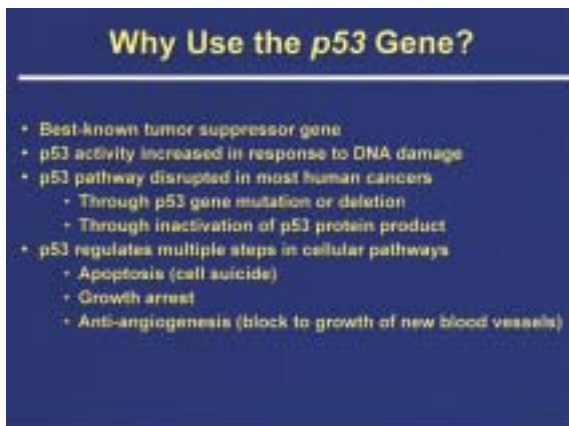


Figure 1

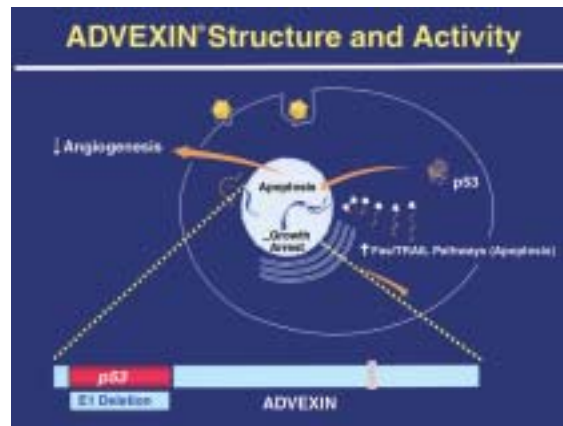


Figure 2

Cancer of the head and neck, while not as common as other types of cancer, presents many unique challenges. Included under this general heading are anatomic sites as varied as the oral cavity, larynx and the paranasal sinuses, each with its own complex anatomy. Because this part of the body is readily visible and also central to many crucial functions, such as speech and swallowing, the aesthetic and functional consequences of head and neck cancer can be devastating. For these reasons, head and neck cancer is best managed by a team of health care professionals derived from the various disciplines typically involved in the treatment of these challenging problems.

At the UConn Cancer Center, the Multidisciplinary Head and Neck Cancer Team has been functioning in this capacity since 1989. To this day, it remains the only prospective, multidisciplinary treatment planning forum of its kind in Hartford County, and one of only two in the State of Connecticut. In addition to the medical specialties of head and neck surgical oncology, medical oncology, and radiation oncology the Team is able to utilize the expertise of the School of Dental Medicine represented by disciplines including oral/maxillofacial

surgery, oral/maxillofacial radiology, oral/maxillofacial pathology, oral medicine, and prosthodontics. Other participants include nutritional and social services, and the services of other disciplines such as neurosurgery or plastic surgery are readily available if needed.

Patients who are seen in consultation by the Head and Neck Cancer Team will typically be examined by all the various participating disciplines during their initial visit. The Team then discusses various treatment options in a conference, and returns to the patients to convey its recommendations. Medical students, dental students and post-graduate trainees in various medical and dental specialties also participate, making the Team conference a valuable educational experience. This multidisciplinary approach greatly facilitates initial treatment planning, and allows the patient and family to be presented with a choice of treatment options, if available. In addition to optimizing coordination of standard therapies, this approach also helps insure patients access to the latest clinical trials and protocols, if applicable.

A variety of clinical trials are available to patients being treated for head and neck cancer at the UConn Cancer

Center. This represents an excellent opportunity for translational and applied research that capitalizes upon the collective expertise of the team. A number of these protocols are managed by the School of Dental Medicine. They address such varied issues as prevention of hypofunction or mucositis following head and neck radiotherapy and the early detection of second primary cancers in patients successfully treated for oral cancer.

In addition, the Cancer Center is a site for such experimental treatment as gene therapy for head and neck cancer.

A significant proportion of head and neck squamous cancers have been shown to be lacking the tumor suppressor gene p53, suggesting that the replacement of this important tumor suppressor gene may be of therapeutic value. An adenovirus vector is utilized to deliver p53 to the tumor via intratumoral injection in those patients randomized to receive the gene therapy product. [Figures 1 and 2] The current gene therapy protocols are limited to patients with recurrent disease that has proved refractory to more conventional therapy and is accessible for direct injection. Protocol T301 randomizes between weekly methotrexate and p53 gene therapy, while T302 randomizes

HEAD/NECK CANCER TRIALS

STUDY	DESCRIPTION	CONTACT
T301	Phase III open-label randomized study to compare the overall survival and safety of bi-weekly intratumoral administration of P53 gene therapy vs weekly methotrexate for squamous cell head/neck CA following progression or recurrence after cisplatin-based chemotherapy; bidimensionally measurable disease N H/N; KPS \geq 60%	Kim Jennings, BA, CCRP
T302	PHASE III open-label randomized study to compare survival and safety of intratumoral P53 gene therapy with cisplatin/5FU vs cisplatin/5-FU alone as first-line chemotherapy for recurrent disease; bidimensionally measurable disease in H/N; KPS \geq 60%	Kim Jennings, BA, CCRP
01-273	Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cevimeline HCl in the treatment of xerostomia secondary to radiation therapy for cancer in the head and neck region	Kathryn Damato, RDH, MS, CCRP
02-147	Phase II double-blind, placebo-controlled, randomized study of celecoxib (SC-58635) in oral premalignant lesions, protocol NQ4-00-02-011	Kathryn Damato, RDH, MS, CCRP
01-105	Evaluation of tolonium chloride (toluidine blue) rinse in the detection of locally recurrent or new primary oral cavity cancers and cancer in situ, protocol ZIL-301	Kathryn Damato, RDH, MS, CCRP
00-082	Cyclooxygenase-2 expression in premalignant oral mucosal lesions	Kathryn Damato, RDH, MS, CCRP

ORAL MUCOSITIS TRIALS

STUDY	DESCRIPTION	CONTACT
02-285	A Phase II, multicenter, double-blind, placebo-controlled, parallel-group, dose-ranging study of the effects of RK-0202 on oral mucositis in patients receiving radiation therapy for carcinoma of the oral cavity, oropharynx or nasopharynx	Kathryn Damato, RDH, MS, CCRP
99-181	RO1 Biobehavioral interventions for oral pain and mucositis	Kathryn Damato, RDH, MS, CCRP

between platinum and 5 fluorouracil chemotherapy alone and in combination with p53 gene therapy.

In summary, the Multidisciplinary Head and Neck Cancer Team at the UConn Cancer Center provides the full range of clinical services needed to care for patients with the complex and challenging problem of head and neck cancer. The program also provides a valuable

educational experience for students and postgraduate trainees and an interface with innovative research protocols.

Patient Appointments—Multidisciplinary Head and Neck Cancer: UConn Cancer Center (860) 679-2100

Study Coordinator—p53 Gene Therapy: Kim Jennings, BA, CCRP, (860) 679-3432, jennings@nso.uhc.edu

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Intensity Modulated Radiation Therapy (IMRT)

By **Robert J. Dowsett, M.D.**
Assistant Clinical Professor
Division of Radiation Oncology
Department of Diagnostic Imaging and Therapeutics

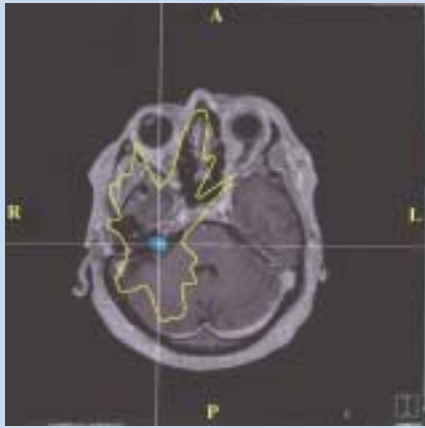


Figure 1:

Axial enhanced reformatted MRI scan image showing IMRT derived dose distribution targeting a right acoustic neuroma (neuroma located at intersection of axes). Note the 100% isodose line (light blue) covering target and the 15% isodose line (yellow) conforming to avoid significant brainstem and eye radiation exposure.

2002 we have treated a total of 143 patients the majority having primary malignant gliomas or metastatic disease to the brain. We recently analyzed our first 10 patients with malignant glioma treated with IMRT following recurrence after conventional radiotherapy. Our one and two year actuarial survival results of 50% and 33% in this group of patients with an extremely poor prognosis is encouraging.

The capability of providing IMRT to a broader cross section of our patients may be close at hand. The new generation of linear accelerators are equipped with integrated MLC systems that can deliver efficient IMRT plans to large radiation fields. Treatment machines such as these and the computers that support them, are being installed in hospitals across the country and region including the University of Connecticut Health Center. The clinical evidence suggesting superior results with IMRT technique is rapidly accumulating in the medical literature.

The Memorial Sloan-Kettering Cancer Center has reported successful dose escalation with IMRT in the treatment of prostate cancer with improved biochemical outcome and lower morbidity compared to patients treated with more conventional techniques (1). It is likely that in the near future IMRT will be the radiation treatment technique of choice for many curative cases of malignant tumors either because of improved efficacy, reduced radiation side effects, or both. IMRT techniques are being shown to be advantageous in many different tumor types and locations. IMRT has been most extensively studied in prostate (1) and head and neck cancers (2), but there is mounting evidence for its use in complex CNS, lung, breast (3), abdominal and pelvic malignancies (4). We hope to expand our use of IMRT as new equipment upgrades make IMRT delivery feasible to larger numbers of patients.

For more information, call Robert Dowsett, M.D. at (860) 679-3225.

Conventional external beam radiation therapy (EBRT) involves the precise targeting of target tissue with multiple intersecting radiation beams. The intensity of each individual beam is relatively uniform across its length and width. Therefore, conventional EBRT technique has limitations in achieving complex three dimensional dose distributions.

Intensity Modulated Radiation therapy (IMRT) is a new and exciting radiation therapy technique that allows the intensity of the beam to be varied. Linear accelerator treatment machines that are capable of delivering IMRT must be fitted with a device that allows modulation of the beam. A multileaf collimator (MLC) is such a device and consists of multiple sliding opposed pairs of metal strips (leaves), which enter and exit the treatment beam according to a preset plan. As the leaves are moved during the treatment, the tissue in the path of "closed" leaves will receive a lower dose intensity and tissue in the path of "open" leaves will receive the maximum radiation dose intensity. Very complex dose distributions can be created by varying the speed and degree of leaf closure for each radiation field. IMRT therefore has the potential to allow the delivery of higher doses of radiation to target tissue while limiting the dose of radiation to adjacent critical normal structures. A new generation of advanced treatment planning computers dictates the movement of the individual leaves for

each radiation field. These computers use inverse treatment planning where the physician specifies the desired dose to the target tissue and dose limits to surrounding normal structures. The movement of the MLC leaves and therefore the dose intensity of the beam is tailored in an attempt to achieve the desired dose distribution.

The University of Connecticut Health Center was the first institution to implement IMRT in the State of Connecticut. Similar technology is currently now available in a limited number of other sites across the state. For the past 7 years the University of Connecticut Health Center has developed considerable experience with IMRT as a radiation technique for both CNS and head and neck neoplasms. A minimultileaf collimator attached to the linear accelerator allows delivery of an elegant intensity modulated plan as specified by a sophisticated treatment planning computer. This first generation IMRT system is best suited for specialized applications in which small complex targets are located adjacent to sensitive normal structures. Common applications at our institution have been the treatment of primary and recurrent primary malignant brain tumors, brain metastases, as well as benign CNS tumors such as acoustic neuromas and meningiomas. In addition, IMRT has been incorporated in the radiation treatment of complex head and neck neoplasms of the nasopharynx and paranasal sinus region. As of August

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New Support Group for Cancer Caregivers

By **Lee Tremback, MSW, LCSW**, Oncology Social Worker and **Donna Pryor, RN, BSN**, Oncology Nursing Director

Janet was becoming angry with her husband because he was in constant pain at home, and then report at the doctor's visit that everything was "fine." Jim was getting "burned out" because his wife refused to allow their daughters or visiting nurses to help with her round-the-clock care. Eric's mother was losing weight rapidly, but refused to eat the home-cooked meals he prepared. These issues and many others are shared by the cancer caregivers that attend the UConn Cancer Center Caregiver Support Group.

Recent literature demonstrates the value of caregiver support groups, which can effectively help caregivers cope with daily stressful demands (1). Participants not only feel satisfied with the group but also experience improvement in coping with personal problems, in psychological functioning, and in having increased support relationships available to them (2). Additionally, studies have shown that health care professionals can facilitate positive outcomes by viewing the family caregiver as a partner in the health care team, providing education and support to the caregiver as they assume this role and evaluating the home care situation (3).

The UConn group began in March 2002 and is facilitated by Donna Pryor, RN, BSN, the Nursing Director for the Cancer Program and Lee Tremback, LCSW, the Oncology Social Worker. On the 2nd and 4th Wednesday nights of each month, the group meets to discuss their frustrations and learn how to cope with their roles as caregivers.

There are increasing demands being placed upon caregivers of cancer patients. Hospital stays are shorter and patients remain at home, even when they require intravenous or other complicated medical treatments. The

support group helps caregivers cope with these stressful demands.

The group also provides an understanding of cancer and cancer treatment. It provides reassurance around managing symptoms and side effects of cancer treatment. The caregivers are educated about the importance of fluids, pain management, fatigue, fevers, bowel changes, depression and many other issues that they encounter on a regular basis.

Due to different outside influences, doctor visits are often brief.

love and laughter. They also receive a great deal of affirmation about their importance in meeting the needs of the patient, along with encouragement to take care of themselves and accept offers of help from others.

We believe that helping caregivers establish a plan of care for themselves is as important as organizing care plans for patients. If your patients' caregivers wish to attend the *UConn Cancer Caregivers Support Group*, please have them contact Lee Tremback, LCSW at (860) 679-2274.



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l to r: Lee Tremback and Donna Pryor

This means that the patient and caregiver must come prepared with written questions so that their time with the physician is utilized effectively. The caregivers are taught how to prepare for visits and are empowered to speak up if the patient is downplaying problems. Physicians cannot help alleviate symptoms if they do not have accurate information from the patient, so the caregivers are taught how to communicate with the doctor without betraying the trust of the patient.

This group is unique because it is strictly for caregivers of cancer patients. This gives the caregivers a chance to express their real feelings. The participants convey a variety of emotions in the group including anger,

IMRT... continued from page 6

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First Year in Review...*continued from page 1*

sponsorship from the Lea's Foundation for Leukemia Research. This series includes the Distinguished Seminar in Cancer Research program, which provides the opportunity for nationally and internationally known scientists and clinicians to give a research and educational presentation at UCHC. Each speaker also devotes at least a day of the visit for discussions with our staff and trainees/students regarding clinical and scientific issues related to his/her work.

In addition to the Dialogue and Seminar Series, we are now systematically developing additional venues for fostering health professional education. Plans for the coming year include initiation of quarterly translational research forums to be held at different geographic locations within the State.

Communication with patients. These efforts are being coordinated with new educational strategies for cancer patients, their families and caregivers. For example, we are now capitalizing on a new partnership with the UCHC Connecticut Health Signature Program that is linked with the several Area Health Education Centers throughout Connecticut. UCHC resources are thus being leveraged across two key Signature Programs to maximize delivery of cancer education to the public. A variety of formats including publications, computer-based information systems and a speaker's bureau are being implemented. We have also created a Cancer Center website that, upon completion later this fall, will act as an important resource for information for cancer families as well as the physicians and other health professionals who provide patient care.

Philanthropic support. We have reached out to our community in a concerted effort to provide information regarding our successes, and to update them regarding

scientific advances we believe are possible with their continued help and financial support. We have been gratified to receive enormous support from our many patients, friends and well-wishers. The UConn Cancer Research Golf Tournament, the Lea Foundation and the Tree of Life program have contributed powerfully in this regard, and we hope to rely on such splendid support from these and other sources in the coming year.

It takes a well functioning leadership team along with a highly committed oncology faculty and staff to fully create and maintain a comprehensive, academically centered approach to oncology. Fortunately, these personnel are on board. This team includes *Dr. Peter Deckers* (Executive Vice-President of UCHC and Dean, School of Medicine), the Associate Directors including *Dr. Robert Bona* (Clinical), *Ms. Judith Kulko* (Clinical Research), *Dr. Douglas Peterson* (Education) and *Ms. Christine Kaminski* (Administrator). The outstanding faculty and staff are too numerous to name individually in this report, but their accomplishments are many. We've had the opportunity to highlight their roles in the recent issues of the *Dialogue*. On behalf of all of my colleagues and on behalf of myself, I thank you for your collegial support this initial year. With your continuing goodwill and support, we shall strive to build UCCC into a nationally prominent center for "*Remarkable Care through Research and Education*" for all cancer patients.

I remain,
Respectfully yours,

Pramod Srivastava, Ph.D.

*Physicians Health Services Chair in Cancer Immunology and
Director, University of Connecticut Cancer Center*



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