UT SOUTHWESTERN MEDICAL CENTER

Puneeth Iyengar, MD, PhD
Assistant Professor
Department of Radiation Oncology
Division of Radiation Biology
Member of Simmons Cancer Center
UT Southwestern Medical Center – Dallas

Contact Information – Clinical Office
NF3.202
Puneeth.Iyengar@utsouthwestern.edu
214-645-7603

Laboratory – NC7.201
214-645-XXXX

Education

	Degree	Year	Field
Massachusetts Institute of Technology, Cambridge, Massachusetts	S.B.	1993-1997	Department of Biology
Albert Einstein College of Medicine, Bronx, New York	M.D., Ph.D.	1997-2005	Cell/Cancer Biology

Residency

University of Texas, Houston Medical Program & MD Anderson Cancer Center, Houston, Texas	2005-2006	Internal Medicine-transitional year
The University of Texas M.D. Anderson Cancer Center, Houston, Texas	2006-2010	Residency, Radiation Oncology

Positions and Honors

2005-2006	Transitional Year Internship, Combined between University of Texas, Houston Medical Program and the University of Texas MD Anderson Cancer Center.
2006-2010	Residency in the Department of Radiation Oncology, UT MD Anderson Cancer Center
2008-2009	Post-doctoral Research Fellow, Cancer Genetics, UT MD Anderson Cancer Center
2010-present	Assistant Professor of Radiation Oncology, Member of Simmons Cancer Center, UT Southwestern Medical Center - Dallas

Honors and Invited Talks

1997-2005 **National Institute of Health Medical Scientist Training Program**

2002 **ECOG Conference for Young Investigators sponsored by Aventis.** Only medical student selected nationally for a spot at the conference and whose work was chosen to give an oral presentation. Adipocyte-Derived Collagen VI Affects Early Mammary Tumor Progression *in vivo*: A Novel Interaction in the Tumor / Stroma Microenvironment.

2002 **Cold Spring Harbor Symposium on Cancer Genetics and Tumor Suppressor Genes.** Only student invited to give talk based on abstract at the symposium (1 out of 40 talks). Adipocyte Effects on Malignant Cells in Breast Microenvironments.

2003 **AACR Conference**. Abstract selected to give short talk. Adipocyte-Derived Collagen VI Affects Early Mammary Tumor Progression *in vivo*: A Novel Interaction in the Tumor / Stroma Microenvironment.

2008 **SABCS** – Poster Presentation - Puneeth Iyengar, Eric A Strom, Yu-Jing Zhang, Gary J Whitman, Wendy A Woodward, Tse-Kuan Yu, and Thomas A Buchholz, M.D. Extended Regional Ultrasound as a Critical Component of the Initial Evaluation of Invasive Breast Cancer

2008 **ASTRO** – Poster Presentation - P. Iyengar, L. B. Levy, S. J. Frank, S. Choi, M. Rex Cheung, A. K. Lee, and D. A. Kuban, Toxicity Associated with Post-operative Radiation Therapy for Prostate Cancer.

2008 **ARS** – Poster Presentation - P. Iyengar, A. Mazloom A. Younes, M. Fanale, F. Shihadeh, and B. Dabaja, M.D. Hodgkin's Lymphoma of the Head and Neck: Characteristics and Outcomes.

2009 **TRS** – Invited Oral Presentation - Puneeth Iyengar, Xiaolan Guo, Thomas A Buchholz, Yibin Deng, and Sandy Chang, Therapeutic Exploitation of Autophagy Pathways Using TERT Inhibition with Radiation in Tumors with p53 Gain of Function Mutations.

2010 **Roengten Resident/Fellow Research Award, MD Anderson Cancer Center**

Inflammation, Cachexia, and Lung Cancer Radiation Therapy Resistance thru Systemic Metabolic Dysregulation

Research Summary

Despite the best efforts of oncologists and scientists, local and distant control rates for lung cancer remain a significant problem. Aside from the inability to diagnose disease at earlier stages, it appears that lung malignancies have a tendency to be treatment refractory to either radiation or chemotherapy/biologics. A significant effort has been undertaken to understand why lung cancers are resistant to systemic therapies. Less emphasis has been placed on learning why some lung cancers are also immune to radiation effects.

Our laboratory's research will be driven by the goal to map out the mechanism of lung cancer radiation resistance. We believe that lung cancers are in part created and driven by the systemic inflammatory states that are common in stress-dependent situations – from external stimuli such as cigarette smoking – to internal stimuli such as cachexia/lipodystrophy that is seen in later stages of disease. Either condition can cause the release of systemic and local acting cytokines that may signal lung cancer cells to behave in certain growth-promoting ways. Our hypothesis is that these molecules may down-regulate tumor suppressive mechanisms in these malignant cells, and by doing so, increase survival despite tumoricidal levels of radiation therapy.

We will take a multi-tiered approach to investigate this hypothesis. Our ultimate goal is to identify novel small molecular weight cytokines that are present in the lung cancer patient "inflammasome" that promote tumor survival despite radiation exposure. Initially, with the use of high throughput mass spectrometry and proteomic techniques, we will characterize the global inflammasome present in human lung cancer patient serum and contrast this profile from the serum of those without malignancy. As part of this evaluation, we will use nanoparticles to enrich for low molecular weight molecules that are often not seen due to their relative inabundance and small weight. We have already begun to study a cohort of patients who received post-operative radiation for Stage III lung cancers by creating tissue microarrays from the surgical specimens and probing them for expression levels of molecules known to be involved in several tumor suppressive pathways – apoptosis, autophagy, senescence, DNA repair, and necroptosis. A correlation will be made with in-field radiation failures and the expression pattern of these various molecules. Concurrently, we will perform *in vitro* studies to tease out how inflammatory conditions alter expression profiles of known and new cytokines from stromal and immune cells that may direct local signaling on tumor cells. Finally, we will validate the importance of newly identified systemic inflammatory molecules in regulating lung tumor development and radiation sensitivity with the use of genetic mouse models and other *in vivo* studies.

Systemic secretory molecules, unique to the inflammatory state found in lung cancer patients as a consequence of cachexic/lipodystrophic, paraneoplastic or/and metabolic dysregulation may be critical in altering radiation sensitivities by influencing intracellular tumor suppressive mechanisms. Our research will attempt to identify and explore the mechanisms by which yet unknown inflammatory proteins induce survival instincts in lung cancer cells despite radiotherapeutic intervention. Blocking the action of these proteins in the future may increase the therapeutic effectiveness of radiation, thereby promoting longer survival in lung cancer patients.

Specific Aims – Goals, Objectives, and Relevance to the National Lung Cancer Partnership funding priorities

Our studies will be focused on understanding how inflammatory molecules secreted in serum can drive lung cancer development, how these very same molecules could cause radiation resistance by acting upon lung tumor cells, and how effectively as clinicians we could block the actions of these molecules in promoting tumor cell death. Specifically, the following aims will drive our endeavors:

1.) to ascertain the proteomic make-up of clinical lung cancer "inflammasomes" by analyzing human serum and tumor tissue expression profiles from multi institutional clinical trials while correlating these markers with increased radiation resistance,

2.) to model stromal inflammatory states, including cachexia, *in vitro* in identifying a mechanism of action for these protein markers on lung tumor cells and to model the influence of inflammation *in vivo* in driving both primary lung tumor development and therapeutic (radiation and systemic therapy) resistance, and

3.) to use the data obtained from the *in vivo* and *in vitro* studies to develop pharmacologic regulators of the molecules deemed critical to effectuating radiation sensitivity. As one can appreciate from our aims, our goals fall within the inherent purpose of the National Lung Cancer Partnership – "research, awareness, **change.**"

Background and Rationale

Ionizing radiation comprises one-third of the approaches taken in treating human malignancies – the other two components being surgery and chemotherapy/biologics. Similar to surgery, radiation is used for improving local control of primary tumors in the definitive setting and for eradicating microscopic disease/positive margins in the post-operative setting. Chemotherapy and biologics are used for systemic control of tumors. These latter agents can also be used as radiation sensitizers. Nearly 60% of all patient malignancies require radiation as part of their overall treatment regimens.

The failure of systemic therapies in the management of cancers is easily apparent by the manifestation of disseminated disease. Failure of local therapies such as radiation, concurrent chemoradiation, or surgery translates into local recurrences or persistent/residual disease. The development of local recurrences can lead to significant morbidity, the potential for seeding of therapeutically resistant disease to distant sites, and mortality. On autopsy evaluations of squamous and adenocarcinoma lung cancer patients, nearly 50% of individuals had prominent loco-regional disease at time of death (1).

Locoregional and systemic failures after treatment with multimodality approaches for lung cancer are significantly higher than for nearly every other cancer pathology and disease site. Lung cancer is the single largest oncologic cause of death in the United States and globally. More people die annually from lung cancer than breast, colon, and prostate cancers combined. Nearly 60% of patients with lung cancer die within 1 year of diagnosis. In 2009, there were approximately 215,000 newly diagnosed cases of lung cancer and nearly 162,000 deaths (2). Five-year overall survival rates approach only 16% for all lung cancer versus 65% for colon cancer, 89% for breast cancer, and 98% for prostate cancer (2). It is primarily due to the diagnosis of lung cancer at relatively late stages (presence of nodal and distant disease) and a general resistance to current therapeutics that leads to the reduced rates of cure for this cancer.

A failure of radiation or concurrent chemoradiation for lung cancer is manifested by resistant residual/persistent disease or local recurrences that can be refractory to further therapy. The rate of local recurrences after radiation can approach 60% for Stage III patients within a five year period. The ultimate question becomes whether persistent disease and local recurrences represent a failure of therapy due to insufficient radiation dose or/and biologically refractory malignant cells (3). At doses normally adequate for high control rates for carcinomas of the head and neck, between 65 and 70 Gy, we do not see the same local control rates for lung cancer. Furthermore, in the post-operative setting, 50-60 Gy is considered adequate for achieving greater than 90% local control for carcinomas of the breast but not so for adjuvant therapy for lung carcinomas. Hence, it is apparent that the dose for lung cancer is not the singular cause for treatment failures. Consequently, it is the inherent biology of lung malignancies that may play a part in their relative radiation resistance.

One of the current hypotheses to explain lung tumor development lies in the concept of inflammation driving genomic instability and subsequent malignancy. Though incompletely validated, inflammation within the context of wound development and repair within the bronchial tree and lung parenchyma is potentially critical as a driving force behind generating the mutations necessary to transform normal cells. It is therefore not a significant stretch to imagine that inflammatory processes may also play a critical role in altering radiation and chemotherapy sensitivities as well. The identity of the systemic inflammatory molecules that may contribute to treatment refractory lung cancer is to this date quite unknown. The very fact that lung cancer, among all lesions, is most associated with paraneoplastic syndromes driven by humoral factors secreted by either the tumor cells themselves or as a consequence of other inflammatory processes adds credence to the possibility that other cytokines may play a role in regulating therapeutic responses (4-29).

Background and Rationale

Tumor suppressive mechanisms including apoptosis, autophagy, senescence, and necroptosis are critical in regulating the balance between cell life and cell death. Any alteration in these mechanisms or shift from baseline may lead to the development of malignancy. Most efforts are aimed at evaluating the cell intrinsic components of these pathways. Less emphasis has been placed on appreciating the context in which extracellular microenvironments and systemic molecules can influence these pathways in making tumors resistant to therapeutics.

Cachexia, defined as the massive loss (up to 80%) of adipose and skeletal tissue, is found in many disease states, particularly cancer. Cancer cachexia is associated with poor performance status and even diminished overall survival. Cachexia accounts for 20-30% of all deaths in patients with cancer and is seen in up to 50% of all cancer patients. Among cancers, lung and gastrointestinal malignancies are associated with elevated rates and extent of cachexia, leading to worse therapeutic disease outcomes. Specifically, in lung cancer patients who have lost a significant portion of their pre-illness weight, there was an 85% decrease in total body fat and 75% decrease in skeletal muscle protein. Part of the failure in treatment is driven by the inability of these patients to receive combined modality treatment –surgery, radiation, and systemics – as part of the standard of care due to poor performance status. Therefore, the oncology community has a challenge in improving the physical state of these patients to promote better therapeutic interventions. Perhaps most importantly, cancer cachexia does not frequently represent an end-stage cancer process, but one that may be present from the beginning of the disease state.

Biologically, there has been some significant progress in attempting to understand how inflammatory processes – both local and systemic – can influence tumor development and progression. Very little has been done to address if and how inflammatory mediators may drive signaling changes in lung tumor cells to become radiation and/or chemotherapy resistant. Our lab is interested in identifying new systemic serum-based molecules upregulated during inflammatory states that may provide the impetus for NSCLCs to become radiation or therapy resistant. *In vitro*, *in vivo*, and clinical studies are being devised to attack these problems.

In many ways, cachexia also represents an altered inflammatory state. With its prevalence so high in lung cancer patients, one must ask whether the general process of cancer cachexia may also be part of the inflammatory cascade that could influence tumor development, progression, and therapeutic effectiveness. The lipolysis of adipose tissue in cachexia and catabolism of muscle into constituent proteins cannot be without repercussions to the primary tumor. Many groups have already demonstrated some cross-talk between tumors and stromal components within the context of the activated microenvironments. No one has determined if inflammatory molecules released during cachexia alter tumor response to radiation, however.

PPARγ is an antidiabetic, anti-inflammatory transcription factor belonging to the superfamily of nuclear receptors. Through the work of a number of groups, PPARγ has been shown to act on adipocytes and muscle cells to reduce inflammatory states and simultaneously promote adipocyte and muscle differentiation. Pre-clinical data supports the notion that PPARγ agonists may reduce the levels of cachexia in mouse models through not as of yet well defined anti-inflammatory mechanisms.

Group Members: Puneeth Iyengar, MD, PhD Prinicipal Investigator
Kalayarasan Srinivasan, PhD Postdoctoral Associate
Narayanan Sriram, PhD Postdoctoral Associate

Journal Research Publications

1.Iyengar P, Combs TP, Shah SJ, Gouon-Evans V, Pollard JW, Albanese C, Flanagan L, Tenniswood MP, Guha C, Lisanti MP, Pestell RG, Scherer PE., **Adipocyte-secreted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization.**, *Oncogene*. 2003 Sep 25;22(41):6408-23.

2.Iyengar P, Scherer PE., Adiponectin/Acrp30, an adipocyte-specific secretory factor: physiological relevance during development**., *Pediatr Diabetes*. 2003 Mar;4(1):32-7.**

3.Cohen AW, Razani B, Schubert W, Williams TM, Wang XB, **Iyengar P**, Brasaemle DL, Scherer PE, Lisanti MP. **Role of caveolin-1 in the modulation of lipolysis and lipid droplet formation**. *Diabetes*. 2004 May;53(5):1261-70.

4.Williams TM, Lee H, Cheung MW, Cohen AW, Razani B, **Iyengar P**, Scherer PE, Pestell RG, Lisanti MP. **Combined loss of INK4a and caveolin-1 synergistically enhances cell proliferation and oncogene-induced tumorigenesis: role of INK4a/CAV-1 in mammary epithelial cell hyperplasia**. *J Biol Chem*. 2004 Jun 4;279(23):24745-56.

5.Iyengar P and Buchholz, TA. **Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer,** *The Women's Oncology Review*. Vol 4, Number 4, December 2004, 293-295.

6.Lin Y, Berg AH, **Iyengar P**, Lam TK, Giacca A, Combs TP, Rajala MW, Du X, Rollman B, Li W, Hawkins M, Barzilai N, Rhodes CJ, Fantus IG, Brownlee M, Scherer PE. **The hyperglycemia-induced inflammatory response in adipocytes: the role of reactive oxygen species**. *J Biol Chem*. 2005 Feb 11;280(6):4617-26.

7.**Iyengar P**, Espina V, Williams TW, Lin Y, Berry D, Jelicks LA, Lee H, Temple K, Graves R, Pollard J, Chopra N, Russell RG, Sasisekharan R, Trock BJ, Lippman M, Calvert VS, Petricoin Iii EF, Liotta L,

8.Dadachova E, Pestell RG, Lisanti MP, Bonaldo P, Scherer PE. **Adipocyte-derived collagen VI affects early mammary tumor progression in vivo, demonstrating a critical interaction in the tumor/stroma microenvironment**. *J Clin Invest.* 2005 Apr 14.

9.Pajvani UB, Trujillo ME, Combs TP, **Iyengar P**, Jelicks L, Roth, KA, Kitsis RN, Scherer PE. **Fat apoptosis through targeted activation of caspase 8: a new mouse model of inducible and reversible lipoatrophy.** *Nat Med*. 2005 Jul;11(7):797-803. Epub 2005 Jun 19.

10.Lara-Lemus R, Liu M, Turner MD, Scherer P, Stenbeck G, **Iyengar P**, Arvan P., **Lumenal protein sorting to the constitutive secretory pathway of a regulated secretory cell.**, *J Cell Sci*., 2006 May 1; 119(Pt9):1833-42.

11.Khan T, Muise ES, Iyengar P, Wang ZV, Chandalia M, Abate N, Zhang BB, Bonaldo P, Chua S, Scherer PE. **Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI**. *Mol Cell Biol*. 2009 Mar;29(6):1575-91.

12.Kumar, PTK, Phoha, VV, Iyengar, SS, and **Iyengar P**. **Reduction of noise due to systematic uncertainties in**
113mIn SPECT imaging using information theory, *Computers in Biology and Medicine*, 39 (2009), 482-488.

13.Y-J Zhang, J Oh, G J Whitman, **P Iyengar**, et al. **Clinically apparent internal mammary nodal involvement in patients with loco-regionally advanced breast cancer- incidence, treatment and outcome**, Accepted in the *International Journal of Radiation Oncology, Biology, and Physics*, 2009.

14.**P. Iyengar**, A. Mazloom A. Younes, M. Fanale, F. Shihadeh, and B. Dabaja, M.D. **Hodgkin's Lymphoma of the Head and Neck: Characteristics and Outcome**s, Accepted in the journal *Cancer*, 2010.

15.A. Mazloom, P.W. McLaughlin, F. Cabanillas, L.E. Fayad, B. Pro, G. Gonzalez, **P Iyengar**, D.L. Urbauer, and B. Dabaja, **Marginal zone lymphoma: factors that affect the final outcome – a study of 275 patients**, Accepted in the *International Journal of Radiation Oncology, Biology, and Physics*, 2010.

16.A. Mazloom, **P. Iyengar**, and B. Dabaja. **Radiation for Hodgkin Lymphoma in Young Female Patients: A New Technique to Avoid the Breasts and Decrease the Dose to the Heart**, Accepted in the *International Journal of Radiation Oncology, Biology, and Physics*, 2010.

17.**P Iyengar**, S Chan, and R Komaki, **Targeting Tumors and Personalizing Individual Treatments for Radiation Therapy**, Book Chapter in *Personalized Therapy for Cancer*, 2010, Accepted.

18.**P Iyengar**, LB Levy, S Choi, et al., **Toxicity Associated with Post-Operative Radiation Therapy for Prostate Cancer**, Accepted in the *American Journal of Clinical Oncology*, 2010.

19.Wu XQ, **Iyengar P**, RajBhandary UL., **Ribosome-initiator tRNA complex as an intermediate in translation initiation in Escherichia coli revealed by use of mutant initiator tRNAs and specialized ribosomes**., *EMBO J*. 1996 Sep 2;15(17):4734-9.

20.Lee H, Volonte D, Galbiati F, **Iyengar P**, Lublin DM, Bregman DB, Wilson MT, Campos-Gonzalez R, Bouzahzah B, Pestell RG, Scherer PE, Lisanti MP., **Constitutive and growth factor-regulated phosphorylation of caveolin-1 occurs at the same site (Tyr-14) in vivo: identification of a c-Src/Cav-1/Grb7 signaling cassette.**, *Mol Endocrinol*. 2000 Nov;14(11):1750-75.

21.Combs TP, Berg AH, Rajala MW, Klebanov S, **Iyengar P**, Jimenez-Chillaron JC, Patti ME, Klein SL, Weinstein RS, Scherer PE., **Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin.,** *Diabetes*. 2003 Feb;52(2):268-76.

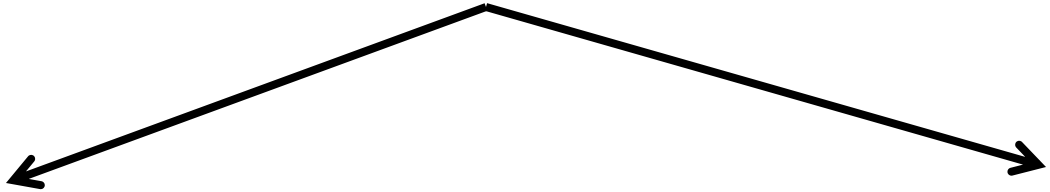
Patents

1. 20090011438 Collagen VI and Cancer 01-08-2009

Board Certifications
The American Board of Radiology - 2011

Professional Associations/Affiliations
American Medical Association
American Society of Clinical Oncology
American Society of Therapeutic Radiology and Oncology
International Association for the Study of Lung Cancer

Inflammation, Cachexia, and Lung Cancer Radiation Resistance thru Dysfunctional Systemic Metabolism



LAB

Biology of Secretory Inflammation

Biology of Inflammation Regulated Radiation Resistance

Biology of Cachexia and its Effect on Radiation Sensitivity

Discovery Biology to Identify New, Candidate Systemic Molecules and Their Role in Regulating Inflammation, Cachexia, and Radiation Response in Lung Cancer

CLINICAL

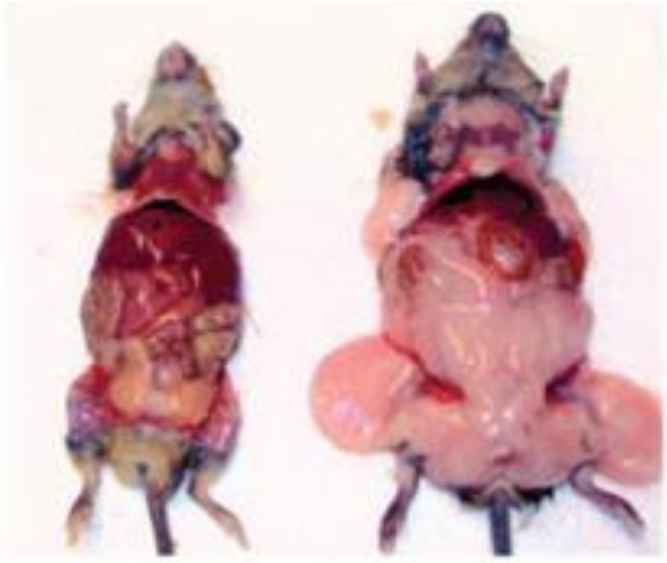
Systemic Inflammatory Profile Ass. with Lung Cancer Radiation Resistance

Systemic Profile of Cachexia and Ass. with Radiation Resistance

PPARγ Agonist for Poor Performance Status NSCLC pts treated with XRT

Potential Mech. for Telomerase Pts.

Puneeth Iyengar, puneeth.iyengar@utsouthwestern.edu



X

+/- XRT

+/- Dimerizer
+/- Myostatin

Kras Lung Cancer Model

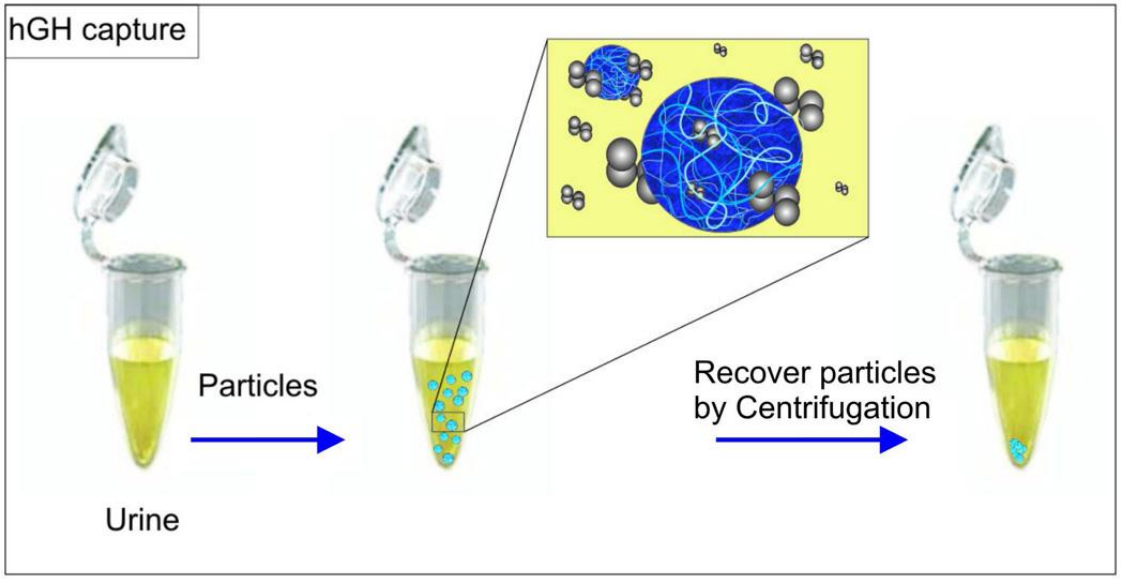
Cytokines Altered as Part of Systemic Metabolic Dysregulation

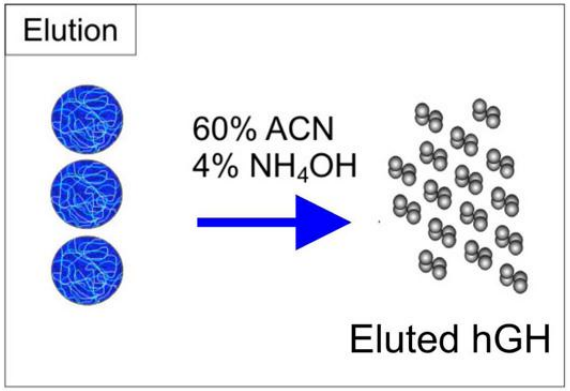
+/- XRT

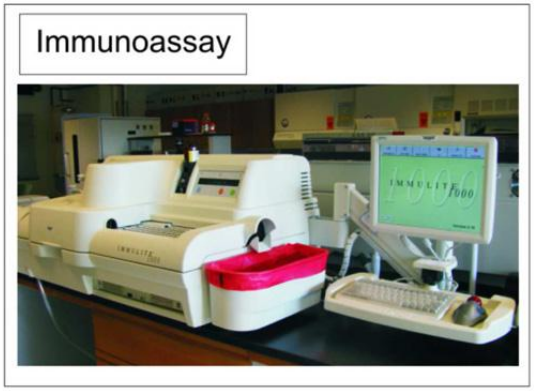
Outcomes

Macrophages
Adipocytes
HBECs
Cancer Ass. Fibroblasts

NSCLC (various SF2 to XRT)
Various genetic backgrounds


hGH capture
Particles
Urine
Recover particles
by Centrifugation


Elution
60% ACN
4% NH4OH
Eluted hGH


Immunoassay

Collaborators

Lance Liotta and Emmanuel Petricoin	George Mason Center for Applied Protoemics
Philipp Scherer	UTSW Touchstone Diabetes Center
John Minna	UTSW Hamon Center for Cancer Therapeutics
Ignacio Wistuba	MD Anderson Cancer Center – Pathology
Hak Choy	UTSW Dept of Radiation Oncology
Ritsuko Komaki	MD Anderson Dept of Radiation Oncology
Joan Schiller	UTSW Chair of Hematology/Oncology
Chaitan Nirodi	UTSW Division of Radiation Biology