Prof. Suresh C. Jhanwar

Biographical Sketch in Brief

I have forty-two years of clinical and research experience and am recognized as a leading cancer geneticist both nationally and internationally. As clinical pathologist, molecular geneticist, served as a director of the clinical diagnostic service in Memorial Sloan Kettering Cancer Center's molecular diagnostic service for 38 years to provide genetic diagnoses for patients treated at the Center. In addition, I also served as a senior Medical faculty member (Attending Geneticist & Cytogeneticist) of the Department of Pathology, Medicine, Human Genetics & Professor of Pathology in the Department of Pathology and Laboratory Medicine of Weill Cornell Medical College, **untill December 2014. During these years, I have also served as Cancer geneticist in various National co-operative groups as well as several clinical trials conducted at the Memorial Sloan Kettering Cancer Center for both hematopoitic as well as solid tumors relating to precision Medicine. Since 2015 I have been appointed as the Member (Professor) Emeritus for life, at the Memorial Sloan Kettering Cancer Center and continue to pursue my research activities.**

My research laboratory was the first one to be designated as the "Laboratory of Solid Tumor Genetics" in 1988. During the years, I have maintained an actively funded and competitive research program, the main focus of which has been to define the role of molecular genetic changes in the etiology, diagnosis**,** progression, and clinical behavior of various solid tumors. In recent years, my laboratory has been engaged in Cancer Genomics, signaling pathways relating to translational application and targeted therapy in Rb and KRAS related malignancies.

PEER-REVIEWED PUBLICATIONS

The results of our research efforts have resulted in approximately 230 full-length publications in high impact Journals such as Cancer Res., Oncogene, New Eng J Med, Science, Nature, Nature Genetics, PNAS, Cell, Blood, EMBO J, J Biol Chem, Mol Cell Biol, J Hum Genet, Clin Cancer Res.

Honors, Awards & Committee Appointments

I also have had the privilege & Honor of delivering the First Hungerford Memorial Lecture established in the memory of the Co-discoverer of the first cancer related cytogenetic abnormality & I have recently been elected as a Foreign Fellow of the oldest Academy of Sciences, India. In addition, I also serve as a Distinguished Visiting Scientist at the Center for Human Genetics, Bangalore India. In the year 2016 I have also joined the NIPD Genetics, Cyprus as a Scientific Consultant and the Cyprus Institute of Neurology and Genetics as a member of the International Scientific Advisory Board.

I am a consultant or served as a scientific reviewer for several funding organizations such as the National Cancer Institute, the Department of Defense, Susan G. Komen for the Cure of cancer and the American Cancer Society, for Grants relating to Programs in Breast Cancer and Genetics of various other cancer types including both hematologic and solid tumors. In the year 2012, I also served as Chairperson for Blood Cancer Panel, DOD.

Teaching, Research Training, & Mentorship

I have trained several PhDs and MDs as part of their post-doctoral training **(seventeen)** and have served as a co-mentor **(twenty eight)** for clinical and research fellows in the laboratory for a period of at least one-two years of research training in Cancer Genetics. In addition, I provided training in cancer genetics to **more than 40** medical/graduate students as well as investigators from various other centers, either from USA or internationally.

I am a member of the editorial boards of several journals including *Anticancer Research*, *International Journal of Human Genetics*, and *Cancer Genomics and Proteomics.*

Patent: RXRG Antagonists for the treatment of Cancer (Xiaoliang L. Xu and Suresh C. Jhanwar) U.S. and international application filed, August, 2011, Published December, 5, 2013.

<u>RESEARCH SUPPORT PAST AND CURRENT</u>: Research efforts of my laboratory during the past several years are supported by financial assistance from the following agencies or organizations.

1. National Cancer Institute research grants.
2. Department of Defense, research programs in breast cancer.
3. Lymphoma Foundations, Inc.
4. Institutional research and development funds.
5. Gerber Foundation.
6. Fund for Ophthalmic knowledge.

Major Highlights of Positions Held, Professional, Academic & Scientific Activities

Prof. Suresh C. Jhanwar

Clinical, Research and Academic Appointments

Clinical
Attending Geneticist & Cytogeneticist
Laboratory Director
Molecular Diagnostic Service
Department of Pathology
Memorial Sloan Kettering Cancer Center
New York, N.Y. 10065

Research
Member and Head
Laboratory of Solid Tumor Genetics
Departments of Pathology and Medicine
Memorial Sloan-Kettering Cancer Center
New York

Academic
Professor of Genetics
Department of Pathology & Laboratory Medicine
Weill Cornell Medical College
New York

Major/Seminal Scientific Contributions

1. Based on gene mapping studies, presented evidence to demonstrate that oncogenes are located at chromosomal sites of specific translocations associated with cancer. **(1982)**

2. Cytogenetic studies were performed, to demonstrate that cytogenetic abnormalities in AIDS related lymphomas are identical to those seen in other lymphomas. **(1983)**

3. Performed one of the earliest studies on molecular analysis of human malignant mesotheliomas to demonstrate that p53 mutation is common in an asbestos induced malignancy of lung – the malignant mesothelioma. **(1991)**

4. Based on a combined cytogenetic and molecular analysis of a large series of tumors from renal cell carcinoma, provided cytogenetic and molecular genetic markers for the various histologic sub-types of carcinomas and also identified genetic abnormalities associated with poor prognosis. **(1991, 1993)**

5. Results of molecular studies performed on sporadic breast cancer, suggested that underlying mutations of BRCA-1 gene are infrequent in sporadic breast and ovarian tumors with Loss of heterozygosity (LOH). **(1994)**

6. Based on combined cytogenetic and molecular studies on a large series of tumors of colorectal carcinoma, a) presented experimental evidence to suggest that uniparental disomy, trisomy or tetrasomy may be a common mechanism to allow expression of mutant alleles of tumor suppressor genes in solid tumors and b) presented data to support that the relative deficiency of chromosome 1p which is commonly deleted in high grade tumors may harbor gene(s), which are associated with progression of the disease in a variety of solid tumor types. **(1995)**

7. Mutations of NF-2 gene are frequently associated with the multistep process of tumorigenesis in malignant mesothelioma. **(1995)**

8. Sporadic breast, ovarian and other cancers with loss of heterozygosity for BRCA-2 do not contain underlying mutation in the second allele. **(1996)**

9. Contributor to a major collaborative study on analysis of mutations in BRCA-2 gene in a large number of Ashkenazi families, demonstrating that an inherited mutation of BRCA-2 is more common among Ashkenazi women than previously estimated. **(1996)**

10. Presented evidence to suggest that, while functional loss of p53 gene often associated with multistep tumorigenesis in malignant mesothelioma is common, it is not always due to point mutation as previously believed, but due to a variety of other mechanisms including uniparental disomy resulting in functional loss of p53 protein**. (2000)**

11. Identified genomic alterations in GIST by array based CGH, which are associated with progression of the disease. **(2004)**

12. In collaboration with Dr. Joseph Testa of Fox Chase Cancer Center, we have recently identified a key mechanism by which Merlin loss-of-function contributes to tumorigenesis in malignant mesothelioma; we have shown that NF-2 behaves as a tumor suppressor gene, i.e., the Merlin controls cell cycle progression by regulating cyclin D1, which in turn may provide unique opportunity for developing targeted therapeutic approaches for a fatal disease. **(2005)** A clinical trial in mesothelioma patients using an mTOR inhibitor in individuals with loss of NF2 is currently being planned.

13. In a recent study on multiple myeloma, an incurable hematologic malignancy of bone marrow plasma cells, we have shown that a cell surface antigen CD32B expressed on clonal plasma cells may serve as target for cytotoxic monoclonal antibody therapy. **(2008)**

14. Retinoblastoma – a childhood retinal cancer serves as a model system to support Knudson's two hit hypothesis of human tumorigenesis. In addition, functional inactivation of Rb gene is also known to play an important role in a variety of other solid tumors. However, there has been a lack of understanding relating to cone-specific signaling circuitry associated with tissue specific multistep tumorigenesis in retinoblastoma. We have recently provided experimental and functional evidence in support for a cone precursor origin of retinoblastoma in which MDM2 and N-MYC expression required for proliferation and survival, and MDM2 expression is further regulated by cone specific TRβ2. **(2009)**

15. Based on a large study which included characterization of 415 tumors and 70 cell lines from colorectal cancer, we have identified clinically significant Exon 4 KRAS mutations, which had high RAS-GTP expression, demonstrated KRAS and MEK dependence and were resistant to EGFR inhibition. **(2010)**

16. Retinoblastoma – a childhood retinal cancer serves as a model system to support Knudson's two hit hypothesis of human tumorigenesis. In addition, functional inactivation of Rb gene is also known to play an important role in a variety of other solid tumors. However, there has been a lack of understanding relating to cone-specific signaling circuitry associated with tissue specific multistep tumorigenesis in retinoblastoma. We have recently provided experimental and functional evidence in support for a cone precursor origin of retinoblastoma in which MDM2 and N-MYC expression required for proliferation and survival, and MDM2 expression is further regulated by cone specific TRβ2. **(Xu et al 2009, Cell, Vol.: 137, 1018-1031)**

17. **Rb-dependent cell cycle progression is by passed in retinoblastoma by thyroid hormone receptor beta 2-mediated Emi1 and SKP2 activation**: in order to investigate the molecular and cellular mechanism underlying the specific role of the transcription factor TRβ2 in retinoblastoma tumorigenesis, we further extended our previously published studies (Xu et al 2009, Cell, Vol.: 137, 1018-1031). The results of such studies suggest that RB1 mutation and the resulting loss of phospho-Rb protein, enables a TRβ1-dependent suppression of Emi1 and SKP2, as a safeguard against RB1-mutant tumor formation. TRβ2 counteracts TRβ1, thus disrupting this safeguard and enabling the development of RB1 mutant tumors. **Cancer Cell (In Revision)**.

18. **RB1 knocked down sustained proliferation of the cells expressing markers of cones but not other retinal cell types**: We previously found that retinoblastoma has properties of a cone precursor tumor and depends on cone-related signaling proteins such as thyroid hormone receptor beta 2 (TRB2), MDM2, and N-Myc. These findings provided strong, yet indirect evidence for a cone precursor retinoblastoma origin. Here, we tested whether human cone precursors are uniquely sensitive to Rb inactivation, in a manner that depends upon cone-specific circuitry, as predicated by the cone origin model. The results of such studies suggest that Rb is required to suppress the proliferation of cone precursors but not other retinal types. As for retinoblastoma cells, the Rb-deficient cone precursor proliferation depended upon the cone factors TRB2, N-MYC, MDM2, and SKP2. RXR-gamma and p130 function as tumor suppressors while p107 is necessary in retinoblastoma tumorigenesis. These findings provide further support for a cone precursor origin of retinoblastoma tumors. **Nature (In Review).**

19. **A).Targeting S phase promoting complex and cell cycle balance by RXRG ligands in the treatment of retinoblastoma and KRAS mutated cancers**: RB1 is often mutated in retinoblastoma, but hyperphosphorylated in KRAS mutated cancers. We previously found that thyroid hormone receptor beta 2 (TRB2) and RXRG played critical role in retinoblastoma pathogenesis via Phospho-Rb, TRB2, and Emi1 based S phase promoting complex (SPC), which was essential for S-phase progression, but it suppressed G2-M transition. In this study, we further sought to investigate the potential role of RXRG in the cell cycle control and targeted therapy of these cancers. RXRG and KRAS were knocked down in retinoblastoma and KRAS mutant colon and lung cancer cells. These cells were treated with RXRG ligands and MEK inhibitor to test for specific responses. Results showed that KRAS knockdown or MEK inhibition in KRAS mutated cancer cells suppressed G1-S transition via Rb dephosphorylation and SPC dissociation. RXRG KD suppressed growth in KRAS activated cancers. RXRG agonist bexarotene promoted SPC dissociation by enhancement of TRB1 activity, causing G1-S arrest in retinoblastoma; whereas RXRG antagonist HX531 prevented TRB2-SPC dissociation by enhancement of TRB2 activity, resulting in G2-M arrest in KRAS activated cancers. HX531 also caused significant DNA separation defect in KRAS mutant cancers, but not in retinoblastoma. Following subconjunctival injection of bexarotene resulted in significant suppression in tumor growth of retinoblastoma in nude mice. We conclude that tumorigenesis requires critical G1-S and G2-M balance, which in turn is regulated by RXRG-TRB2-SPC and RXRG-TRB1-APC/cdh1. Retinoblastoma exhibits a G1-S transition defect, whereas KRAS activated cancer exhibits G2-M defect, which are synthetic lethal defects and serve as targets of RXRG ligands. Thus, RB1 and KRAS activated cancers require specific cell cycle balances, therefore, different therapeutic strategies by RXRG ligands **(2011-2013)**.

B).Thyroid hormone receptor beta 2-mediated PTTG1 activation prevents chromosome instability induced by Rb deficiency in retinoblastoma.
Genomic instability is the hall mark of several RB1 deficient cancer types, except human retinoblastoma. We tested whether cone specific thyroid hormone receptor beta 2 (TRB2) known to regulate tumorigenesis, and PTTG1 a mitotic checkpoint protein that helps to keep sister chromatids together play role in maintaining genomic stability in retinoblastoma.
TRB2 is highly expressed in cone precursors and anterior pituitary gland. SNP analysis showed that cone-derived retinoblastomas displayed few genomic copy number changes. TRB2-KD in retinoblastoma cells downregulated PTTG1, increased genomic instability (GIN) and aneuploidy, but TRB1-KD stabilized PTTG1 accumulation. PTTG1-KD resulted in cell cycle arrest and aneuploidy, which promoted the TRB2-KD induced cell cycle arrest and aneuploidy, but partially rescued TRB1-KD induced effects. Medium RB1-KD on the other hand, caused Rb hyperphosphorylation and PTTG1 accumulation, whereas deep RB1-KD caused PTTG1 degradation in osteosarcoma and neuroblastoma cells. CDK4/6 inhibition assay showed that phospho-Rb is necessary to stabilize the PTTG1. Pituitary tumors in Thrb2-/-::*Rb1*+/- mice showed more aneuploidy than those in Thrb2+/+::*Rb1*+/- mice.
These results show that phospho-Rb is necessary for PTTG1 stabilization and genomic stability. Relatively stable genome in retinoblastomas is maintained by TRB2-mediated PTTG1 stabilization, counteracting Rb deficiency related GIN in retinoblastoma and pituitary tumors.

Committee Appointments:

1. Scientific Consultant in Cancer Cytogenetics/Genetics, National Cancer Institute, Bethesda, Maryland.

2. Scientific Reviewer in Medical Genetics and Cancer Cytogenetics/Molecular Genetics, Department of Defense, Maryland **(CML, Hematologic Cancer, Breast-Ovarian, Prostate cancer and Neurofibromatosis related cancers).**

3. Scientific Reviewer, Susan G. Komen for the Cure Grants Program in Breast Cancer.

4. Scientific Reviewer, Genetic Mechanism of Cancer, American Cancer Society.

5. Scientific Reviewer, NCI Intramural Research Program, Bethesda, Maryland.

6. Scientific Reviewer, Technology Transfer Fellowship Applications, UICC, Geneva, Switzerland.

7. Co-Chairman and Member, International Working Group on MDS Cytogenetics, MDS Foundation.

8. Chair, Advisory Board, Future Trends in Molecular Oncology Testing, Abbott Molecular, April, 201

9. Chair, Blood Cancer panel, Department of Defense, congressionally directed Medical Research program, 2012.

Licensure in Sub-Specialty

Laboratory Directors License from the New York Sate Department of Health In:

1. Cancer Cytogenetics.

2. Genetic Testing (Cancer).

3. Oncology Molecular and Cellular Tumor markers.

PROFESSIONAL MEMBERSHIPS:

Member/Officer	Name of Organization	Dates Held
Member	American Society for Cell Biology	1984-2002
Member	American Society of Human Genetics	1984-present
Member	American Association for Cancer Research	1987-present
Member	American Association for the Advancement of Science	1992-2010
Member	Connective Tissue Oncology Society	1991-1993
Member	European Cytogeneticists Association	1999-2001
Member	American Society of Hematology	1999-present
Member	International Cytogenetics and Genome Society	2002-present

HONORS AND AWARDS:

1. International evaluation committee member for the Ph.D. program in medical genetics and molecular medicine, the Cyprus Institute of Neurology and Genetics, Cyprus, 2011-2012.

2. **Foreign Fellow of the National Academy of Sciences, India, 2010.**

3. Delivered the 24th Annual **" Foundation Day Lecture"** of the National Institute of Immunology, New Delhi, India, October 6, 2010.

4. **Distinguished Visiting Scientist, Center for Human Genetics, Bangalore, India, 2010-.**

5. Co-Chairman, International Working Group on MDS Cytogenetics, Chicago, October 21-23, 2007.

6. Course Director, Fluorescence In Situ Hybridization (FISH) Workshop, MSKCC, 2005.

7. Certificate of Recognition for Human Genetics Teaching at the Sarah Laurence College, Human Genetics Program, 2002.

8. Symposium Chairman at the 18th UICC International Cancer Congress, Oslo, Norway, 2002.

9. Symposium Co-Chairman at the International Congress on Invasion and Metastasis, Athens, Greece, 2001.

10. President, Executive Committee of the Alumni Society of the Memorial Hospital for Cancer and Allied Diseases, 1998.

11. **First David Hungerford Memorial Lectureship at the Center for Human Genetics, Bangalore, India, 1998.**

12. Symposium Co-Chairman at the International Cancer Congress, Delhi, India, 1994.

13. Pre-Congress Course Director, 5th International Symposium on colorectal cancer, Turin, Italy, 1991.

14. Distinguished Scientist Lectureship at the College of Medicine at the University of South Alabama, 1989.

15. National Research Service Award Fellowship, NIH, 1978-1980.

Editorial Board Membership:

In Vivo (1992-1994)
Journal of Genetics (1999-present)
Cancer Genetics and Cytogenetics (1995-99)
AntiCancer Research (1994-present)
Cytogenetic and Genome Research (2000-2005)
International Journal of Human Genetics (2000-present)
Cancer Genomics and Proteomics (2008-present)

Consulting Editor: (1998-present)

Scientific Reviewer for research articles submitted for publication to journals such as: American Journal of Human Genetics; Cancer Research; Clinical Cancer Research; Carcinogenesis; Cytogenetics and Cell Genetics; Cancer; Genes, Chromosomes and Cancer; Journal of Genetics; Gynecologic Oncology; Genomics, International Journal of Cancer, Leukemia Research etc.

Mentor for Training in Cancer Genetics:

1. The laboratory provided post-doctoral as well as clinical fellowship training to **Ph.D. and/or MD, Ph.D. candidates**, most of whom are practicing physicians either in academic/clinical medicine or independent researchers in the USA or internationally.
2. Provided training in **cancer genetics to 30 medical/graduate students** as well as investigators from various other centers, either from USA or internationally.

Prof. Suresh C. Jhanwar
Departments of Pathology and Medicine
Memorial Sloan-Kettering Cancer Center

History of collaborations, joint workshops and other scientific activities in India

(1) Workshop on "In situ molecular hybridization using oncogene probes", at the Cytology Research Center, Indian Council of Medical Research, New Delhi, India, April 15-24, 1986, Course Director: Dr. Usha K. Luthra **(Course Consultant)**

(2) "WHO Workshop on Advanced Methods in Cytogenetics and Molecular Genetics", organized at The All India Institute of Medical Sciences, New Delhi, India, January 1-12, 1990, Course Director: Dr. Kiran Kucheria **(Course Consultant)**

(3) Workshop on "Fluorescent in situ hybridization in medicine and biology" at the Indian Institute of Science, Bangalore, January 2-8, 1993; Center for Cellular and Molecular Biology, Hydrabad, India, January 11-14, 1993, Course Director: Dr. H. Sharat Chandra **(Invited Faculty)**.

(4) UNESCO Regional Training course on the Molecular Genetics of some Blinding Diseases, held at L.V. Prasad Eve Institute, Hyderabad and the Indian Institute of Science, Bangalore, India, December 14-22, 1998, Course Director: Dr. D. Balasubramanian (**Guest faculty).**

(5) “Workshop on Fluorescence In Situ Hybridization in Oncology” at the Center for Human Genetics, Bangalore, February 2-4, 2004, Workshop Director: Dr. H. Sharat Chandra **(Guest Faculty).**

(6) Served as a scientific reviewer for theses submitted by candidates from All India Institute of Medical Sciences, Delhi, Gujarat Cancer Center, Ahemedabad, and National Institute of Mental Health and Neuro Sciences, Bangalore, for Doctor of Philosophy.

(7) Member, International Scientific Advisory Panel, for the Indian Society of Medical and Pediatric Oncology.

(8) Sponsored several geneticists and oncologists from India for UICC Technology Transfer as well as Varoon Mahajan Foundation Fellowships for training at MSKCC, New York.

(9) Served as an Invited Speaker to various National and International conferences held in India on a regular basis.

(10) Distinguished Visiting Scientist, Center for Human Genetics, Bangalore, India.