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BIBLIOGRAPHY SKETCH IN BRIEF:

I have thirty-eight years of clinical and research experience and am recognized as a leading cancer cytogeneticist/geneticist both nationally and internationally. As a clinical cytogeneticist/geneticist, and director of Memorial Sloan Kettering Cancer Center's cytogenetics laboratory (up until December 2013), I have been responsible for supervising the cytogenetic and molecular cytogenetic evaluation of 6,000 clinical samples each year to help diagnose patients with hematopoietic and solid tumors. I also developed and directed strategic planning for the laboratory's technologies, validation of newer molecular cytogenetic tests including array/SNP based cancer specific Comparative Genomic Hybridization assays, instrumentation, staffing, budget, and regulatory issues. As an Attending Geneticist and Cytogeneticist and Director of Cancer Cytogenetics, 80% of time was devoted to patient care, 10% research activities, 5% administration and remaining 5% teaching and mentoring students, fellows and junior faculty. **In addition, as a Cancer geneticist and member of Molecular diagnostic service with certification from the New York State-Department of Health in Cancer cytogenetics, Molecular oncology and Predisposition cancer genetics, I also served as a key member of various disease management teams and actively participated in various clinical trials for both hematologic as well as solid tumors**.

My research laboratory was the first one to be designated as the "Laboratory of Solid Tumor Genetics" based in the department of pathology in 1988. During the years, I have maintained an active and competitive research program, the main focus of which has been to define the role of molecular genetic/cytogenetic 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 related malignancies, the results of such research efforts are **briefly outlined in the section "Major contributions"** and have been published in high impact journals like PNAS, Science, Nature, Nature Genetics, NEJM, Blood, Oncogene, MCB, Cancer Research, Cell, EMBO among others resulting in more than 225 publications.

I also have had the privilege of serving as a course director or symposia chair at various national and international conferences, and have delivered the First Hungerford Memorial Lecture established in the memory of the Co-discoverer of the first cancer

related cytogenetic abnormality. In recognition of my contributions In Cancer Genetics, Molecular Biology and Genetic Medicine, I have recently been elected as a Foreign Fellow of the oldest Academy of Sciences, India, which in the past 30 years elected only 84 such fellows internationally.

I have trained several PhDs and MDs as part of their post-doctoral training **(seventeen)** and have served as a co-mentor **(approximately thirty)** for clinical and research fellows rotating through the laboratory. In addition, I provided training in cancer genetics to more than **thirty eight** medical/graduate students as well as investigators from various other centers, either from the USA or internationally. **I also serve as a Professor of Pathology in the Department of Pathology and Laboratory Medicine of Weill Cornell Medical College.**

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 and recently also Chaired the Blood Cancer Panel for DOD.

I am a member of the editorial boards of several journals including *Anticancer Research*, *International Journal of Human Genetics*, and *Cancer Genomics and Proteomics*, and am a scientific reviewer for research articles submitted to a number of journals such as the *American Journal of Human Genetics; Cancer Research; Clinical Cancer Research; Carcinogenesis; Cytogenetics and Cell Genetics;* and *Cancer*. I am a member of the American Society of Human Genetics, American Society of Hematology, and American Association for Cancer Research.

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

RESEARCH SUPPORT PAST AND CURRENT: 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 Scientific Contributions

1. Provided cytogenetic evidence for the infertility in men, which is due to abnormal meiosis resulting in asynapsis and spermatogenic degeneration **(1980)**.

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

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

4. 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)**

5. 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)**

6. 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)**

7. 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)**

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

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

10. Participated in a 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)**

11. 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 loss of expression and complete absence of functional p53 protein. **(2000)**

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

13. 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).**

14. 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).**

15. **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 TRß2. **(2009).**

16. 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)**

17. **Rb-dependent cell cycle progression is by passed in retinoblastoma by thyroid hormone receptor beta 2-mediated Emi1 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 **(2011-2013)**.

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 **(2011-2013).**

19. **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 hyper-phosphorylated 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)**.

20. **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 **(2012-2013)**.