

## Novel Role for orphan receptor PXR in Cancer

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The nuclear receptor pregnane X receptor (PXR) is activated by a range of xenochemicals, including chemotherapeutic drugs, and has been suggested to play a role in the development of tumor cell resistance to anticancer drugs. PXR also has been implicated as a regulator of the growth and apoptosis of colon tumors. Here, we have used a xenograft model of colon cancer to define a molecular mechanism that might underlie PXR-driven colon tumor growth and malignancy. Activation of PXR was found to be sufficient to enhance the neoplastic characteristics, including cell growth, invasion, and metastasis, of both human colon tumor cell lines and primary human colon cancer tissue xenografted into immunodeficient mice. Furthermore, we were able to show that this PXR-mediated phenotype required fibroblast growth factor (FGF) 19 signaling. PXR bound to the FGF19 promoter in both human colon tumor cells and “normal” intestinal crypt cells. However, while both cell types proliferated in response to PXR ligands, the FGF19 promoter was activated by PXR only in cancer cells. Taken together, these data indicate that colon cancer growth in the presence of a specific PXR ligand results from tumor-specific induction of FGF19. These observations may lead to improved therapeutic regimens for colon carcinomas.

### Biography

Sridhar Mani (Shri) is a Professor of Medicine and Genetics at the Albert Einstein College of Medicine, Bronx, NY. He was the Founding Director of the Phase I Experimental Therapeutics Program at the Montefiore/Einstein Cancer Center. He received his MD degree (1990) from the Mount Sinai School of Medicine, New York, NY followed by further postdoctoral training in Internal Medicine (Board Certified)(1990-1992) and Hematology/Oncology (Board Certified, Onc 1992-1995) at Yale-New Haven Hospital, Yale University School of Medicine, New Haven, CT. Subsequently, he was the program leader for gastrointestinal oncology at the University of Chicago, Chicago, IL. During his tenure as a medical student, he did summer work at Rockefeller and then as a postdoctoral fellow at Yale, he studied under Dr. Eric Fearon on the role of DCC in colon cancer. In 1998, he returned to NY (Albert Einstein College of Medicine) to develop a Phase I Program in Oncology and a laboratory effort on drug metabolism. He is the recipient of the Clinical Investigator Award from the Damon Runyon Foundation (New York) and presently is an NIH funded Investigator on the role of orphan nuclear receptors in metabolism. He is a permanent member of the Developmental Therapeutics Study Section of NCI and serves as an editorial board member for Cancer Research, Clinical Cancer Research and Molecular Cancer Therapeutics (AACR). He has more than 100 peer-reviewed papers in journals like Science, Cancer Research, Clinical Cancer Research, Molecular Pharmacology, Molecular Endocrinology, Molecular Cancer Therapeutics, and Journal of Clinical Oncology.