Novel Approaches to Pancreatic Cancer Drug Development

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Despite several advances in the radiological assessments and extensive chemotherapeutic testing for number of decades, the overall five-year survival of all patients diagnosed with pancreatic cancer is still only 2% to 3%. The lack of progress against this malignancy is thought to be due to no early diagnosis and striking therapeutic resistance. Like other epithelial cancers, pancreatic cancer is thought to evolve through pancreatic intraepithelial neoplasia (PanIN), and these lesions progress to pancreatic ductal adenocarcinomas (PDAC). The gatekeeper mutation for pancreatic cancer is KRAS, with loss of tumor suppressor genes such as CDKN2A, p53, and Smad4/Dpc4 lead to PanIN lesions progress to carcinoma *in situ* and invasive PDAC. Characterization of KRAS transgenic mice models provided unique opportunity to develop chemopreventive strategies for the pancreatic cancer prevention. To prevent or delay PanINs to PDAC, we tested gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, nitric-oxide releasing aspirin (NO-ASP), a modified synthetic NSAID and curcumin, a naturally-occurring NSAID in conditional LSL-$Kras^{G12D/+}$ transgenic mice. Transgenic Kras mice at PanIN 2 and PanIN 3 stages exposed to two dietary doses levels of Gefitinib (100 and 200 ppm), NO-ASP (1,000 and 2,000 ppm) and Curcumin (1,000 and 2,000 ppm) for 35 weeks. At termination, pancreases were evaluated histopathologically for PanINs and PDAC, and various biomarkers were measured by immunohistochemistry, immunofluorescence, immunoblotting, and/or reverse transcription-PCR. Dietary gefitinib at 100 and 200 ppm significantly suppressed PDAC incidence by 77% and 100%, respectively ($P < 0.0001$) when compared with control diet. Similarly, both NO-ASP and curcumin suppressed PDAC incidence, albeit without dose-response effect. Importantly, a significant inhibition of carcinoma and a suppression of PanIN 3 were were observed in mice treatment groups. Also, agents such as gefitinib reduced EGFR, proliferating cell nuclear antigen, cyclin D1, C2GNT, RhoA, β-catenin, p38, phospho-extracellular signal–regulated kinase, caveolin-1, and mucin and increased cyclin B1 in the pancreatic lesions/PDAC. In summary, these results show that cancer drug development strategies targeting Pan IN 3 (in situ carcinomas) progression to PDAC represents novel approach for pancreatic cancer treatment. {Supported by NCI-CN-53300 and Kerley-Cade Endowment}

Currently, Dr. Rao is the Kerley-Cade Endowed Chair in Cancer Research, Distinguished Professor of Medicine, in Medical Oncology, and Director of the Center for Chemoprevention and Cancer Drug Development, PCS Oklahoma Cancer Center, at the University of Oklahoma Health Sciences Center (OUHSC) in Oklahoma City. Rao holds the appointments at the Graduate School (Professor) and Department of Pathology (adjunct Professor). Also, he is the Leader of the Aerodigestive tract Cancers/Chemoprevention Program (2004 to 2009) and Chairman of the Scientific Advisory Committee (2006-2009) at the PCS Oklahoma Cancer Center. Dr. Dr. Rao earned his M.S. (1983) and Ph.D. (1987) degrees in Microbiology from the Osmania University, Hyderabad, India. Dr. Rao joined the OUHSC 2004. Previously he held the Chief, Division of Nutritional Carcinogenesis and Leader of Chemoprevention Program at the American Health Foundation (AHF)-Cancer Center, an NCI-designated Cancer Center, Valhalla, New York. Dr. Rao joined AHF-Cancer Center in 1988 as a Senior Research Fellow and appointed in 1992 as a Member American Health Foundation Cancer Center (AHF-CC) and Section Head of the Division of Nutritional Carcinogenesis and by 2001, he came up through the ranks to become Division Chief, and Cancer Center Program Leader of Chemoprevention and Nutritional Carcinogenesis.

Dr. Rao is currently the principal investigator (six) or the co-principal investigator (one) on NIH/NCI grants (Three R01s, Two N01s, one RAPID, and one R21) with totaling >$14 million, focused on chemoprevention and cancer drug development on several of areodigestive tract cancers. Also, he has been PI and Co-PI on previously awarded NIH/NCI peer-reviewed funding totaling over $42 millions. Dr. Rao is a member of the Board of Scientific Counselors/Reviewer of the National Cancer Institute Study Sections and Special Emphasis Panels. He is part of Nutrient-Gene interaction and Cancer Chemopreventive Drug Development Think Tank and the Review Panel for NCI-CADRG, Division of Cancer Prevention at the National Cancer Institute.

Dr. Rao is the Associate Editor and editorial board member of many pharmaceutical and cancer research journals. He has lectured broadly and internationally in his areas of interest and expertise. Dr. Rao has over 160 peer reviewed research publications in leading scientific and cancer research journals (>8,300 Citations; with average of 79 citations/citied article with h-index:43). He has mentored a large number of graduate students and post doctoral fellows and has a large laboratory, including a number of research and tenure track Assistant Professors.