Dr. E. Premkumar Reddy obtained his Ph.D. in 1971 from Osmania University, Hyderabad and carried out his post-doctoral training at the UCLA School of Medicine from 1972-1974 and later at the National Cancer Institute from 1974-75. He worked at the National Cancer Institute first as an independent investigator and later as a section chief between 1975 and 1984. In 1984, he moved to Hoffmann La Roche and held appointments at Hoffmann La Roche and the Roche Institute of Molecular Biology as a Full Member. In 1986, he joined the Wistar Institute as a Professor and Deputy Director. From 1992 to 2010, he served as the Director of the Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia. He joined the Mount Sinai School of Medicine in March of 2010 as a Professor in the Departments of Oncological Sciences and the Department of Structural and Chemical Biology and as the Director of Experimental Cancer Therapeutics.

While working at the National Cancer Institute, he made a number of seminal discoveries that provided a clear understanding of the molecular basis of cancer. He cloned and sequenced a number of viral oncogenes which included *abl*, *ras*, *fgr*, *mos, myb, myc* and *sis* oncogenes and their cellular homologues which pinpointed the precise changes that cellular proto-oncogenes undergo to produce cancer-causing viral oncogenes. He extended this work to human cancers and was responsible for the seminal discovery that point mutations in the cellular *ras* genes result in their oncogenic activation. His work also showed the mechanisms associated with the activation of *Abl* and *Myb* oncogenes, which are associated with the development of human myelogenous leukemias. His recent work on cell cycle regulator, Cdk4 has shown that this gene is very critical for the development of ErbB2 and ras oncogene-induced tumors and inhibition of expression of Cdk4 causes ablation of breast cancers caused by ErbB2 and Ras oncogenes.

Dr. Reddy has pioneered the development of small molecule inhibitors targeted against oncogenes and cell cycle regulators for cancer therapy. One of the drugs developed by Dr. Reddy, ON01910 is currently in Phase III clinical trials and has shown profound clinical activity in MDS (Myelodysplastic Syndrome) patients as a single agent. In combination with Oxaliplatin and Gemcitabine, ON01910 was found to have remarkable efficacy in reducing the tumor burden of several metastatic cancers including breast, ovarian and pancreatic cancers. In addition to ON01910, Dr. Reddy has developed six different cancer drugs, two of which (ON013100, and ON01210) have entered clinical trials and the other three are expected to enter clinical trials in the next one year. Two of these drugs, a small molecule inhibitor of Plk2, ON1231320 and a second compounds ON123300 which is a dual inhibitor of Cdk4 and AKT pathways are currently undergoing pre-clinical evaluation.

Dr. Reddy founded the cancer journal Oncogene in 1986 and served as its Editor from 1986 to 2009. In 2010, he founded a second cancer journal, Genes & Cancer for which he currently serves as the Editor-in-Chief. According to the data published by the Institute of Scientific Information, which compiled the list of most highly cited authors, Dr. Reddy was amongst the top 0.5% of the authors in the world.

Targeting Cancer with a Selective ATP-Competitive Inhibitor of PLK-2 Kinase Activity

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ABSTRACT

The Polo like kinases play key roles in mitosis. While the upregulation of PLK1 in cancer is well documented and PLK3 has been demonstrated to be a tumor suppressor, little is known about the oncogenic significance of PLK2. PLK2 kinase activity is essential for centriolar duplication and is also believed to play a regulatory role in the survival pathway by physically stabilizing the TSC1/2 complex in tumor cells in hypoxic conditions. Protein tyrosine hyper-phosphorylation and the upregulation of serine/threonine kinases associated with cell cycle progression have been linked to the etiology of cancer. In our attempt to identify ATP-mimetic compounds that are cytotoxic against a panel of cancer cell lines, we identified several sulfonyl pyridopyrimidines that possess nanomolar activity. The most potent of these compounds, ON1231320, was found to be a specific PLK2 inhibitor when profiled against a panel of 288 wild-type, 55 mutant and 12 special kinases. Further *in vitro* testing revealed that ON1231320 is a selective inhibitor of PLK2 with no inhibitory activity against PLK1, PLK3 and PLK4. Confirmation of this interaction and its selectivity was obtained from pull down studies using lysates of tumor cells and a biotinylated analog of ON1231320. The cytotoxic effect of the drug is mediated by apoptosis as evidenced by the induction of Caspase 3/7 activity and by the cleavage of PARP in a dose dependent manner. ON1231320 affects cell cycle progression by blocking tumor cells in the G2/M phase however it does not affect normal human fibroblasts. ON123120 exhibits an excellent safety profile with no overt signs of toxicity, no loss of body weight and 100% survival in mice given a single subcutaneous dose of 200 mg/kg. Our ongoing efforts include efficacy studies in nude mouse models, identification of the structural determinants of the interaction between ON1231320 and PLK2 by computational and crystallographic methods and the identification of novel PLK2 substrates to elucidate its role in cancer biology.