

4th World Congress on

Cancer Science & Therapy

October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore Conference Center, USA

MDM2 Mediated cancer angiogenesis and novel anti-angiogenic agents

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Angiogenesis plays a very important role in controlling the tumor growth and metastatic progression. Evidently, the angiogenic mechanisms are often regulated by the microenvironment that surrounds the tumor, thorough the use of hypoxia inducible transcription control process and release of growth factors such as VEGF. Though the tumor angiogenesis is regulated by a wide range of intracellular mechanisms, the role for MDM2 in controlling tumor angiogenesis and metastasis has been slowly evolving. Our recent studies have established a strong link between MDM2 and VEGF transcription control mechanisms. Also, interference with the function of the Vascular Endothelial Growth Factor Receptor (VEGFR) has become one of the main strategies to obstruct tumor growth by blocking pro-angiogenic signals. In this respect, several anti-angiogenic blockers are currently available with a wide range of specificities and mechanisms. Many of these anti-angiogenic drugs are either monoclonal antibodies with certain specificity towards neutralizing pro-angiogenic factors or small molecules with an ability to block VEGFR related kinases. However, through molecular modeling approach two new anti-angiogenic drugs were designed at the Rumbugh Goodwin Institute for Cancer Research of NSU to interfere with the binding sites of VEGFR rather than inhibiting the receptor associated kinases. A novel isoindol-amide compound code named F16 and a second compound with a structure that is analogous to purine moiety were identified as new competitive antagonists for VEGF. Both the F16 and JFD have strong anti-angiogenesis potentials since different concentrations (0 to 10 μ M) of the experimental drugs can inhibit the tube formation by HUVEC cells on EC-MatrixTM gel. Receptor binding assay with Fluorokine conjugated VEGF in HUVEC cells has also confirmed a strong competitive binding ability for both F16 and JFD (0.001 to 1.0 μ M) in a dose dependent manner. The new drugs also show strong anti-cancer effects in athymic nude mice that are implanted with GI-101A breast tumor. Interestingly, the combination treatment with Taxol was more effective in the xenograft tumor model compared to mono-therapies with F16, JFD or Taxol alone. Results so far clearly suggests that F16 and JFD can specifically inhibit VEGF binding to VEGFR2 and reduce phosphorylation that can eventually prevent endothelial cell proliferation and tumor angiogenesis. Furthermore, the results from the *in vivo* experiments are very conclusive and support the fact that these two small molecules can inhibit tumor growth by blocking VEGFR. At present both *in vitro* and *in vivo* experimental results are strong enough to validate F16 and JFD as promising anti-angiogenic agents with significant therapeutic potential.

Biography

Dr. Rathinavelu joined NSU in 1992 and is currently holding the Associate Dean for Institutional Planning and Faculty Development position at the College of Pharmacy. He is also serving as the Executive Director of the Rumbaugh Goodwin Institute for Cancer Research (RGI). Dr. Rathinavelu was able to initiate his cancer research in 1993 and from that time onwards his research efforts are focused on discovering new therapeutic targets and novel drugs for cancer treatment. He has published nearly 50 peer-reviewed research articles, serves on the editorial board of scientific journals and has conducted peer review of several scientific manuscripts for publications. He has also co-authored a text book, written two book chapters and presented more than 75 scientific papers in National and International conferences. Among other scientific achievements, so far Dr. Rathinavelu has received four patents, one for the discovery of novel assay methods to measure kinases and phosphatases in biological samples. In the spring of 2011 he received 2 patents for the two newly discovered anti-cancer drugs, named F16 and JFD that can starve the cancer and shrink them through anti-angiogenic mechanisms. In the Spring of 2014 one of his anti-angiogenic drugs received the Japanese patent also. Dr. Rathinavelu and his team are planning to enter into collaborative agreements with pharmaceutical companies and take these drugs to early stage clinical trials.

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