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Inhibition of AXL kinase reverses the mesenchymal phenotype in leukemia cells through the disruption of retinoic acid signaling

Mesenchymal stem cells (MSCs) contribute to the regeneration of mesenchymal tissues and are essential in providing support for the growth and differentiation of hemopoietic cells within the bone marrow microenvironment. It is becoming increasingly clear that the tumor microenvironment plays a very important role in tumor progression and drug resistance, and the selection of cancer cells possessing the mesenchymal phenotype leads to drug resistance in many different tumor types. We have been exploring the role of the protein AXL in promoting the mesenchymal phenotype in both myeloid and lymphoid malignancies, and the role of AXL in promoting drug. The signaling downstream of AXL that leads to the acquisition of the mesenchymal phenotype has not been well elucidated. Following results from a genetic screen using a zebrafish model, we have discovered a role for retinoic acid (RA) signaling which is regulated by AXL and controls the mesenchymal phenotype in leukemic cells. We have demonstrated that treatment with our AXL inhibitor, TP-0903, disrupts RA signaling and leads to a reversal of the mesenchymal phenotype. Following TP-0903 treatment, we interrogated changes in mRNA expression using RT-PCR, protein expression using standard immunoblotting, and endogenous RA levels using an ELISA. We also assessed the effect of TP-0903 on tumor growth in an in vivo model of AML in which TP-0903 strongly inhibited xenograft tumor volumes by up to 100% with multiple dose levels and treatment schedules. Biomarker modulation correlated well with efficacy in xenograft tumors following treatment. Based on these findings, TP-0903 was further evaluated in acute leukemia models with acquired resistance to FLT3 inhibitors and chronic leukemia cells with resistance to BTK inhibitors. TP-0903 is entering a first-in-human Phase I clinical trial in solid cancer patients and we anticipate a hematological malignancy Phase I to follow.

Biography

Steven L Warner, PhD, is the Vice President of Discovery and Development at Tolero Pharmaceuticals. He specializes in small molecule drug discovery, new screening platforms in drug discovery, and translational research focusing on cancer therapeutics. He is an expert in the discovery of novel cancer agents and has played integral roles in moving multiple compounds into clinical trials. He has a broad background in molecular and cell biology that comes from over a decade of involvement in drug discovery and development in both academic and pharmaceutical industry settings. He earned his Graduate degree in Pharmaceutical Sciences at the University of Arizona. He completed a Post-doctoral fellowship under the mentoring of Dan Von Hoff at the Translational Genomics Research Institute (TGen). He has held leadership positions in drug development teams, including at SuperGen Inc. and the Huntsman Cancer Institute where his responsibilities ranged from initial compound library screens to proof-of-concept studies in animal models. He worked with the Center for Investigational Therapeutics at the Huntsman Cancer Institute as Senior Manager, Drug Discovery. Together in these capacities, he has led or integrally participated in drug discovery projects that have produced six first-in-man clinical compounds and has published several peer-reviewed publications and patents from multiple drug discovery projects.

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