OMICS Group Conferences
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International Conference on
Emerging Cell Therapies

October 1-3, 2012 DoubleTree by Hilton Chicago-North Shore, USA

Bcl-2 Antagonists: Targeted therapeutics in chronic lymphocytic leukemia

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B-CLL is presently an incurable disease representing the most common form of leukemia in North America and Europe. Unlike other cancer cells which are inherently driven by uncontrolled proliferation, CLL cells are exclusively compelled through defective apoptosis. High levels of Bcl-2 family anti-apoptotic proteins are primarily responsible for defective apoptosis and are considered major targets of cancer therapy development. Among several approaches to inhibit Bcl-2 family proteins including small molecule inhibitors and antisense oligonucleotides, use of BH3 mimetics that bind to BH3 domain of anti-apoptotic proteins is a mechanistic approach of targeting Bcl-2 proteins. Naturally occurring polyphenols (gossypol) appear to be potent Bcl-XL inhibitors, giving the plausible molecular explanation for the anticancer activity of these agents. In CLL, gossypol restored apoptosis via caspase independent, AIF-mediated mechanism. Its relative toxicity due to presence of two reactive aldehyde groups led to synthesis of gossypol analog, apogossypol (AT-101) that is more stable than gossypol with low nM binding affinity to all three anti-apoptotic proteins (Mcl-1, Bcl-2 and Bcl-xl). In CLL, AT-101 induced caspase independent apoptosis and demonstrated ability to overcome stromal mediated protection over apoptosis. Apogossypolone, synthesized with modifications in aldehyde groups, demonstrated low nM binding to Mcl-1 and Bcl-2 but not Bcl-XL. As a proof of concept, structure based BH3 mimetic ABT-737 demonstrates ability to induce apoptosis in a variety of cancer cells. Its oral compound ABT-263 has proven substantial susceptibility of CLL cells through Bcl-2 inhibition. Results of a Phase I Study of Navitoclax (ABT-263) in patients with relapsed or refractory disease warrants Bcl-2 as a valid therapeutic target in CLL. Thus, molecules that mimic pro-apoptotic BH3 domains represent a direct approach to overcoming the protective effects of anti-apoptotic proteins such as Bcl-2 and Bcl-XL.

Biography

Balakrishnan has obtained her Ph.D from Madras University, India and postdoctoral studies from MD Anderson Cancer Center, Houston, TX. She is a faculty member of Graduate School of Biomedical Science (GSBS), and an associate faculty member of Experimental Therapeutics Academic program (ETAP), Houston TX. She holds associate member position in the Faculty1000. She has published more than 20 papers in reputed journals and serves as an editorial board member of journal "Frontiers in Hematology Oncology". Dr. Balakrishnan research is focused on identifying novel therapeutic agents for the treatment of leukemia, in particular for CLL, by understanding the metabolism, mechanism of action, and interactions with other therapies. The goal is to implement new agents in the clinic for the treatment of CLL.

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