World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:9, No:04, 2015

Small Molecule Inhibitors of PD1-PDL1 Interaction

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Abstract : Studies on tumor genesis revealed a number of factors that may potentially serve as molecular targets for immunotherapies. One of such promising targets are PD1 and PDL1 proteins. PD1 (Programmed cell death protein 1) is expressed by activated T cells and plays a critical role in modulation of the host's immune response. One of the PD1 ligands - PDL1- is expressed by macrophages, monocytes and cancer cells which exploit it to avoid immune attack. The notion of the mechanisms used by cancer cells to block the immune system response was utilized in the development of therapies blocking PD1-PDL1 interaction. Up to date, human PD1-PDL1 complex has not been crystallized and structure of the mouse-human complex does not provide a complete view of the molecular basis of PD1-PDL1 interactions. The purpose of this study is to obtain crystal structure of the human PD1-PDL1 complex which shall allow rational design of small molecule inhibitors of the interaction. In addition, the study presents results of binding small-molecules to PD1 and fragment docking towards PD1 protein which will facilitate the design and development of small–molecule inhibitors of PD1-PDL1 interaction.

Keywords : PD1, PDL1, cancer, small molecule, drug discovery
Conference Title : ICBBMB 2015 : International Conference on Biochemistry, Biophysics and Molecular Biology
Conference Location : Lisbon, Portugal
Conference Dates : April 16-17, 2015