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# Structure and function of perforin, pathophysiology of human perforin deficiency and perforin inhibitors as potential therapeutics

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**Abstract**

Perforin is a 67kDa pore-forming protein secreted by CTL/NK cells to induce the death of virus-infected and transformed cells; its role is indispensible for granule-bound serine proteases (granzymes) gaining access to the cytosol of target cells to instigate apoptosis. Congenital perforin deficiency leads to a fatal immunoregulatory disorder, hemophagocytic lymphohistiocytosis (FHL Type 2) (1). Recently, we solved the crystal structure of monomeric perforin, elucidated the cryo-EM structure of the entire pore, defined functions of the various domains and determined the molecular mechanism of oligomer assembly. We also showed that partial loss of perforin function, particularly through inheritance of the very common hypomorphic A91V allele may predispose to hematologic cancer in adolescents and young adults (2-5).

While the complete and long term loss of perforin function can result in fatal immunosuppression, its temporary pharmacological inhibition may be desirable in certain immune-based pathologies. Our laboratory expresses and purifies potently active recombinant perforin in baculovirus-infected insect cells, enabling us to screen for small molecular 'drug like' perforin inhibitors. As a result, we identified the dihydrofuro[3,4-c]pyridone family (among other lead series) as possessing potent perforin-inhibitory activity, with a capacity to block both purified perforin and perforin-dependent NK cell-mediated target cell death (6,7). We have used various techniques to demonstrate that the compounds exert their inhibition by direct perforin binding. Potential scenarios in which perforin inhibitors may be useful will be discussed, in particular the protection of allogeneic bone marrow stem cells from transplant rejection in the context of cancer

**Biography**

Professor Joe Trapani received his medical degree in 1977 and his PhD in 1985, from The University of Melbourne and The Royal Melbourne Hospital. He completed physician training (FRACP) in Rheumatology (1985) and received his PhD in the immunogenetics of HLA-associated disease, particularly B27-related arthropathy. Joe Trapani is Executive Director Cancer Research, Peter MacCallum Cancer Centre, Melbourne, where he co-heads the Cancer Immunology Program. Professor Trapani's research interests include the immunopathology of viral and auto-immune diseases, apoptosis induction by cytotoxic lymphocytes and cancer immunotherapy, and he has authored more than 240 research papers, reviews and book chapters on these topics.