Perforin – a novel drug target in cancer and transplantation medicine

A collaborative team of researchers at Monash University and the Peter MacCallum Cancer Centre have identified lead candidate perforin inhibitors that could moderate unwanted immune responses in cancer therapy, diabetes and organ transplantation. The team has determined the crystal structure of perforin and performed a fragment based drug discovery screen to identify lead inhibitors. This knowledge could form the basis of a rational drug development program for creating small molecule based therapeutics. The team is also developing monoclonal antibodies that may be of clinical utility as perforin inhibitors.

Benefits over existing therapies:

- Potential to develop ‘First in Class’ small molecule therapeutics to improve the success of transplantation therapies.
- Differentiated mechanism of action that is upstream of incumbent targets with potential for high efficacy and less side effects.
- Potential for therapeutic utility across a wide-range of immune-mediated diseases.

Background

The pore-forming immune effector perforin is an essential weapon of the immune system. It is produced and secreted by cytotoxic T-lymphocytes (CTL) and natural killer (NK) cells in order to destroy virally-infected or oncogenic targets.

However, unwanted perforin function is central to the failure of certain transplantation therapies and pathogenesis of serious diseases. For example, residual host NK activity in patients mediates graft destruction and the high mortality rate (~30%) of patients receiving allogeneic bone marrow transplantation therapy for leukaemia.

There is also strong evidence that perforin-dependent CTL function is responsible for pancreatic islet destruction in diabetes and graft rejection in organ transplantation.

Currently, there is no drug that specifically and effectively inhibits perforin-dependent NK or CTL function.

Until recently, the molecular basis for perforin pore formation remained unclear, and furthermore, no crystal structure was available to guide lead inhibitor development. The team has surmounted these challenges and has determined the crystal structure of perforin with a lead inhibitor bound.

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The opportunity

Our team has made world-leading progress in determining the crystal structure of perforin (Figure 1) and in understanding the molecular basis of pore formation.

With the support of the Wellcome Trust, the team has validated perforin as a drug target and developed the appropriate animal models and clinical trial strategy for assaying human perforin inhibitors in vivo during bone marrow transplantation therapy. They are currently working on three lead classes of perforin inhibitors based on the structural information and part of the results of fragment-based drug discovery screens.

However, there is a significant body of data that was not investigated in the work funded by the Wellcome trust. These data include several distinct chemical scaffolds that likely bind to alternative sites on perforin.

In addition, target sites on perforin, derived from crystal structure data, make attractive extracellular targets for monoclonal antibody (mAb) drug development. Monash researchers have access to tier 1 facilities (MATF), assays, reagents and models that complement their knowledge of target/disease biology, and support the development of therapeutic grade neutralising anti-human perforin mAbs.

We are seeking a partner to create and test new compositions that could inhibit perforin function at alternative binding sites. Monash researchers have deep expertise in determining the structure and binding mechanism of perforin and potential inhibitors through crystallography and electron microscopy.


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