Consequences of pharmacological inhibition of cathepsin C using IcatC\textsubscript{XPZ-01} on maturation of granzyme zymogens in cytotoxic lymphocytes

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Granzymes are serine proteinases present in cytotoxic lymphocytes and involved in elimination of virus infected and cancerous cells. As other related immune cell serine proteinases, granzymes are matured \textit{in vitro} by a cysteine proteinase called, cathepsin C (CatC). However, biochemical characterization of granzymes A and B in cytotoxic lymphocytes from Papillon-Lefèvre syndrome (PLS) patients with CatC deficiency allowed the highlighting of a CatC independent processing and maturating pathway. Patients with PLS retained significant granzyme activities (~50-60\%) in cytotoxic lymphocytes and displayed normal cytotoxicity against cancer cells (1). These results suggested that CatC is not the unique proteinase involved in the maturation of pro-granzymes in human lymphocytes. The presence of CatC-like proteinase(s) might provide a molecular explanation for the lack of a generalized cytotoxic T-cell activity in patients with PLS. Pharmacological targeting of CatC using a nitrile cell permeable inhibitor (IcatC\textsubscript{XPZ-01}) (2) resulted in ~50\% of Granzyme B inhibition in cytotoxic T-cells, showing that CatC-independent maturation was not altered.

References:
