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Structure-based design of IL-17 antagonists

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Statement of the Problem: IL-17A is a pro-inflammatory cytokine that is implicated in many autoimmune and inflammatory diseases. Disruption of interactions between IL-17A and its main receptor, IL-17RA may be effective in treating these diseases. Monoclonal antibodies targeting pathway of IL-17A have shown significant efficacies in treating psoriasis and psoriatic arthritis over existing therapies. To develop non-antibody IL-17A antagonists, structure information of IL-17A, its complex with IL-17RA and inhibitors are valuable. To develop non-antibody based IL-17A antagonists, we identify peptides, small molecules and fragment leads through various techniques. We designed and produced well behaved IL-17A and IL-17RA, and obtained crystal structures of IL-17A and IL-17RA. These structures provide the structural basis for IL-17A signaling through IL-17RA. We then move on to determine the structures of IL-17A in complex with peptide and small molecule antagonists. Since both peptide and small molecules disrupt the native structure of IL-17A and hinder crystallization, to achieve these structures we used FAB of an IL-17A targeting antibody as a crystallization chaperon to stabilize IL-17A/peptide and IL-17A small molecule complexes. Furthermore, we conducted fragment screen using large numbers of high diffracting apo IL-17A crystals, and identified two binders. These structures enabled us to understand the structural basis of IL-17A signaling, identify lead materials and design IL-17A antagonists with much improved potencies.

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