

## MS6-P10 Crystal structure of the human IL-17AF heterodimer

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IL-17A and IL-17F are the best characterized and most closely-related members of the IL-17 family which also includes IL-17B, C, D, and E. These pro-inflammatory cytokines bind to a heteromeric receptor complex composed of the IL-17 receptor A (IL-17RA) and the IL-17 receptor C (IL-17RC) to mediate host protection against infections, while also contributing to the pathogenesis of various autoimmune diseases.<sup>1</sup> IL-17A and IL-17F share 50% sequence identity and are known to function as homodimers. Nevertheless, they can also form a biologically active heterodimer, IL-17AF,<sup>2-4</sup> which also signals through the IL-17RA/IL-17RC receptor complex,<sup>5</sup> but whose physiological role is still largely unknown. We have determined the crystal structure of human IL-17AF at 2.3Å resolution. Like IL-17A and F, IL-17AF is a disulfide-linked dimer, with the two protein chains associated in a parallel manner. Both subunits show the expected cystine-knot fold with two intrachain disulfide bridges. The core of the dimer interface is mainly defined by one pair of anti-parallel  $\beta$ -strands from each chain and involves many hydrophobic residues conserved across IL-17A and F. Additionally, the N-terminal segments of each protein chain reach the other subunit across the dimer interface, thus providing extensive additional contacts. Besides their similar overall topology, the IL-17RA receptor binding sites are highly conserved between the hetero- and homo-dimeric forms.<sup>6-8</sup> In human IL-17AF, however, a hydrophobic pocket that is essential for IL-17RA recognition is occluded in the IL-17F subunit by a phenylalanine residue (Phe18) of the N-terminal region of IL-17A. Interestingly, while this binding site is also occupied by two phenylalanine residues (Phe10 and Phe11) in the IL-17F homodimer it is freely accessible in the IL-17A homodimer.<sup>6,8</sup> This hydrophobic lock may thus be an important structural element in modulating IL-17RA receptor binding and may contribute to the distinct binding affinities of this receptor for the different IL-17A/F isoforms.<sup>5</sup> **References** 1. Wei J & Chen D (2013) *Emerging Microbes & Infections* 2, e60. 2. Chang SH, Dong C (2007) *Cell Res*; 17(5): 435-40. 3. Liang SC et al (2007) *J Immunol*; 179: 7791-7799. 4. Wright JF et al (2007) *J Biol Chem*; 282: 13447-13455. 5. Wright JF et al (2008) *J Immunol*; 181: 2799-2805. 6. Hymowitz SG et al (2001) *EMBO J*; 20(19): 5332-41. 7. Ely LK et al (2009) *Nat Immunol*; 10(12): 1245-51. 8. Liu S et al (2013) *Nat Commun*; 4 :1888.

**Keywords:** IL-17, cytokine, structure

## MS7. Nucleic acids and their complexes and assemblies with proteins

Chairs: Miquel Coll, Christine Cardin

### MS7-P1 Structural basis for the inhibition of CCL2-signaling by a mirror-image aptamer

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The crystal structure of a 40mer mirror-image RNA oligonucleotide completely built from nucleotides of the non-natural L-chirality in complex with the pro-inflammatory chemokine L-CCL2 (monocyte chemoattractant protein 1), a natural protein composed of regular L-amino acids, will be reported (Oberthuer, 2014). The L-oligonucleotide is an L-aptamer (a Spiegelmer®) identified to bind L-CCL2 with high affinity, thereby neutralizing the chemokine's activity. CCL2 plays a key role in attracting and positioning monocytes; its overexpression in several inflammatory diseases makes CCL2 an interesting pharmacological target. The PEGylated form of the L-aptamer, NOX-E36 (emapticap pegol), already showed promising efficacy in clinical Phase II studies conducted in diabetic nephropathy patients. The structure of the L-oligonucleotide•L-protein complex was solved and refined to 2.05 Å. It unveils the L-aptamer's intramolecular contacts and permits, in combination with binding studies, a detailed analysis of its structure-function relationship. Furthermore, the analysis of the intermolecular drug-target interactions reveals insight into the selectivity of the L-aptamer for certain related chemokines. Oberthuer, D. et al. Crystal structure of a mirror-image L-RNA aptamer (Spiegelmer) in complex with the natural L-protein target CCL2. *Nat Commun* 6, 6923 (2015).

**Keywords:** CCL2, aptamers, L-RNA, chemokines, drug-target interactions