

MS05-04 | STRUCTURAL BASIS FOR CD96 IMMUNE RECEPTOR RECOGNITION OF NECTIN-LIKE PROTEIN-5, CD155

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CD96, DNAM-1, and TIGIT constitute a group of immunoglobulin superfamily receptors that are key regulators of tumor immune surveillance. Within this axis, CD96 recognizes the adhesion molecule nectin-like protein-5 (necl-5), although the molecular basis underpinning this interaction remains unclear. We show that the first immunoglobulin domain (D1) of CD96 is sufficient to mediate a robust interaction with necl-5, but not the DNAM-1 and TIGIT ligand, nectin-2. The crystal structure of CD96-D1 bound to the necl-5 ectodomain revealed that CD96 recognized necl-5 D1 via a conserved “lock-and-key” interaction observed across TIGIT/necl complexes. Specific necl-5 recognition was underpinned by a novel structural motif within CD96, namely an “ancillary key”. Mutational analysis showed that this specific residue was critical for necl-5 binding, while simultaneously providing insights into the unique ligand specificity of CD96.