Contortion of the oncogenic protein LMO2 structure in vivo by a single VH domain antibody causes functional inhibition

Helen Sewell¹, Tomoyuki Tanaka¹, Kamel El Omari², Erika J Mancini², Abimael Cruz-Migoni¹ and Terence Rabbitts¹
¹Leeds Institute of Molecular Medicine, Leeds, United Kingdom ²Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom

LMO2 is an essential transcription factor for the regulation of haematopoiesis and comprises two zinc-binding LIM domains that mediate interactions with other proteins such as LDB1 and TAL1. Translocations involving LMO2 are present in approximately 9% of patients with T-cell acute lymphoblastic leukaemia (T-ALL), however aberrantly expressed LMO2 has been shown to be present in more than 60% of T-ALL samples. In response to this, we have developed a single VH domain antibody that binds Lmo2 inside cells and inhibits tumourigenesis in an Lmo2-dependent leukaemia model. We have solved the crystal structure of LMO2 in complex with the anti-LMO2 VH to determine the mechanism of functional inhibition by the VH. The LMO2 structure is made up of disordered loops in between short β-sheets and α-helices with the first 26 N-terminal residues being completely disordered. Comparing the structure of LMO2 in complex with either the anti-LMO2 VH or with LDB1 shows a significant conformational difference, specifically in the relative positioning and angle between the two LIM domains. These findings suggest a model in which initially synthesized LMO2 protein is intrinsically disordered and binding to a partner protein confers structure that dictates subsequent protein complex formation. The effect of the anti-LMO2 VH is to contort LMO2 into a conformation that interferes with the binding of natural partners, thereby restricting the formation of functional transcription factor complexes. The anti-LMO2 VH is a starting point for a new type of therapeutic approach for the treatment of LMO2-dependent leukaemia.