The current paradigm for the role of NRP1 in angiogenesis is VEGF binding to NRP1 and VEGFR2, promoting NRP1/VEGFR2 complex formation and enhancing VEGFR2 signalling. However, the biological importance of neither VEGF NRP1 binding, nor NRP1 in VEGFR2 signalling have been defined. To address these questions we investigated NRP1-dependent VEGF chemotactic signalling, and performed structural and functional analysis of the NRP1 VEGF-binding domain. We show that NRP1 plays a selective role in VEGFR2 chemotactic signalling through its cytosolic domain, and further identify NRP1 as a major node in the stimulation of growth factor signalling through the adapter protein p130Cas in endothelial, vascular smooth muscle and tumour cells. Furthermore, we mapped the NRP1 VEGF binding site through mutational analysis and solving the structure of the b1 domain co-crystallised with a specific small molecule antagonist of VEGF binding to NRP1. NRP1 b1 domain mutations, eg Y297A, which result in complete loss of VEGF binding cluster in the antagonist binding groove, and overexpression of Y297A NRP1 inhibited VEGF binding, disrupted NRP1/VEGFR complexation, selectively inhibited VEGF signalling, and inhibited migration towards a VEGF gradient and VEGF-induced branching angiogenesis in a co-culture cell model. These findings provide the basis for an improved understanding of how NRP1 functions in VEGF signalling and angiogenesis, and also highlight a key role for NRP1 as a major hub in chemotactic signalling via diverse receptor tyrosine kinases.