The extracellular region of the TrkA receptor consists of five domains: two cysteine rich domains (d1&d3), a leucine rich domain (d2) and adjacent to the membrane, two immunoglobulin-like domains (d4&d5). We have shown that the NGF binding region on the TrkA receptor resides in TrkAd5. This domain was expressed in *Escherichia coli* purified and the structure determined.

NGF is a major mediator of inflammatory pain, neuropathic pain and asthma. We have shown that TrkAd5, sequesters NGF with picomolar affinity, thus representing a novel therapeutic agent. TrkAd5 has proven efficacious in two animal models of interstitial cystitis and two models of asthma, indicating that the development of small molecule NGF antagonists would be desirable.

In Alzheimer’s disease cholinergic dysfunction in the brain is associated with memory loss. Cholinergic neurons express the TrkA receptor, and a large body of evidence suggests that TrkA agonists should prevent these cells from degenerating.

We have used the three dimensional co-ordinates of the NGF-TrkAd5 structure to screen virtual libraries of small molecule drug like compounds. Compounds predicted to bind have been synthesised and tested in an in vitro \([I^{125}]\)NGF receptor binding assay. Several different families of compounds have been identified which disrupt NGF-TrkA binding.