Poster Presentation

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Understanding RET receptor tyrosine kinase ligand recognition and chemical inhibition

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The RET receptor tyrosine kinase is crucial for embryonic and adult development, with mutations in both the extracellular and kinase domains leading to several types of cancer. In order to understand the mechanisms of RET activation in more detail, we have investigated how RET interacts with its bipartite ligand comprising of a glial cell line derived neurotrophic factor (GDNF) family ligand and a GDNF family receptor (GFRalpha). To visualise this interaction, we have reconstituted two vertebrate RET ternary complexes containing both ligand and co-receptor and have determined a pseudo-atomic model for a mammalian RET ternary complex using electron microscopy. Our structures reveal the basis for ligand recognition and will be presented. As RET is a validated anti-cancer target, we are actively investigating RET chemical inhibitors in collaboration with several chemistry laboratories. We have determined structures of a diverse set of chemical scaffolds bound to RET leading to an improved RET pharmacophore based on crystallographic, biochemical and cell-based data. As current FDA-approved drugs for RET-dependent metastatic thyroid cancer suffer from off-target dose-dependent toxicity and lack of specificity, we hope our data will usefully contribute to the design of second generation RET chemical inhibitors.

[1] *Knowles P et al, J Biol Chem. 2006 Nov 3;281(44):33577-87*

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