TARGET-SPECIFIC ASSAY SERVICES

Kinase mutant panel performed with ^{33}PanQinase™ assay technology.

➢ RET Kinase $_{H658-S1114}$ Mutant Panel

Ret proto-oncogene

Synonyms: CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET51, RET-ELE1

RET is a receptor tyrosine kinase which is the catalytically active part of the signaling complex for the glial cell line-derived neurotrophic factor family of ligands. Gain-of-function mutations in RET are implicated in human cancers1. Several physiological RET mutations have been described, RET and its mutants seem to be promising oncological targets for small molecule kinase inhibitor-based therapies 2.

Wild type RET as well as nine pathophysiologically relevant RET mutants are available as recombinant human active protein kinases and for compound testing services (Figure 1; see also reverse side).

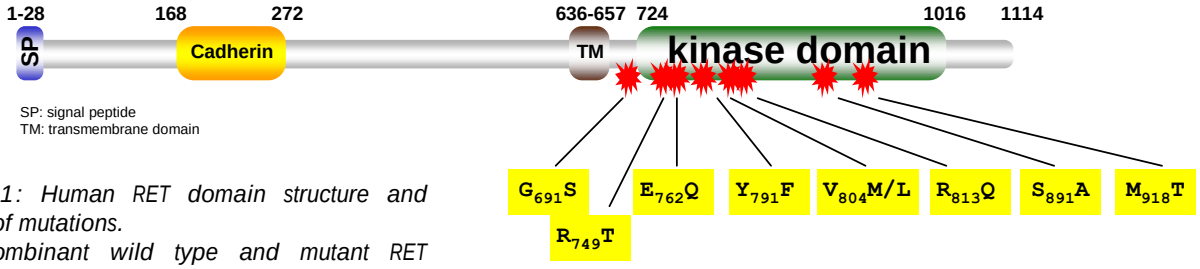

Figure 1: Human RET domain structure and position of mutations.
The recombinant wild type and mutant RET proteins comprise amino acids H658-S1114.

Side-by-side comparison of wild type RET and RET mutants

Wild type RET and nine different RET mutants were compared side-by-side with respect to inhibition by the reference inhibitor BIBF1120 (Vargatef) (Figure 2). IC50 determinations of BIBF1120 (Vargatef) were performed at corresponding app. ATP-Km (see Table 1) using our radiometric ^{33}PanQinase Assay™.

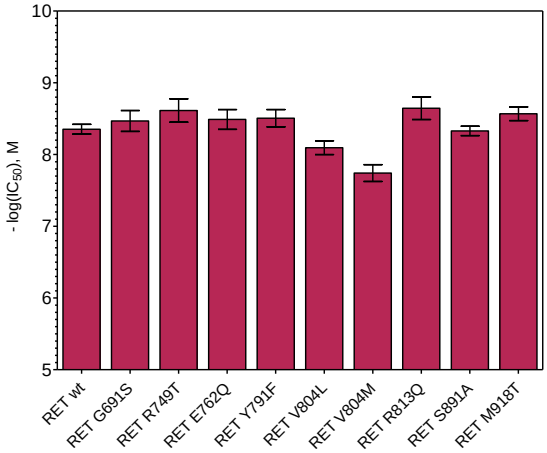

Figure 2:
Differential inhibition of 10 RET variants by the inhibitor BIBF1120 (Vargatef) at app. ATP Km (n= 2).

References
[1] Structure and chemical inhibition of the RET tyrosine kinase domain: P. P. Knowles et al., J. Biol. Chem. 281, 33577-33587 (2006)
[2] Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors, F. Carlomagno et al., Oncogene 23, 6056–6063 (2004)