THERAPY

**GTPASE RAL—A NEW
TUMOUR TARGET**

Novel small molecules can inhibit the activity of the Ras-like GTPases RalA and RalB and suppress tumour xenograft growth in mice, new research demonstrates.

Ras mutations are implicated in the development of many human tumours, but drugs that target Ras or its downstream signalling pathways have poor clinical efficacy. In a novel approach, reported in *Nature*, Dan Theodorescu and colleagues investigated inhibitors of Ral proteins, which are part of another Ras signalling pathway and have a role in proliferation and metastasis in many cancers, including prostate and bladder tumours. “The starting point was a hypothesis—inactive Ral has a cavity that collapses on activation and, as Ral cycles between inactive and active states, blocking Ral in the inactive form should be therapeutically viable,” explains Theodorescu.

Virtual protein-structure-based screening of 500,000 molecules identified 88 compounds that could bind to the cavity and *in vitro* assays demonstrated that three of these molecules (RBC6, RBC8 and RBC10) blocked the activation of RalA and cell migration. Further structural analysis and chemical synthesis to improve the protein–molecule interaction resulted in BQU57, an RBC8-derived compound with increased inhibitory activity.

Next, the team evaluated the specificity of RBC8 and BQU57 for the Ral pathway and found that cell anchorage and growth—processes mediated by Ral proteins—were only inhibited in cells that were Ral-dependent and that the effect was lost when *RAL* expression was knocked down using small interfering RNAs (siRNAs).

In vivo, using subcutaneous tumour xenograft models, RBC8 and BQU57 demonstrated good pharmacokinetic properties and could be detected in tumour tissues 3 h after intraperitoneal injection. Importantly, administered over a period of 21 days at a dose of 50 mg/kg, both compounds inhibited tumour growth at a level similar to siRNA-mediated knockdown of *RALA* and *RALB*.

“As we march towards clinical development, we are investigating ways to improve the potency of these compounds and determining useful drug combinations,” says Theodorescu. “In addition, we are looking at defining the companion biomarkers for patient selection.”

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Original article Yan, C. *et al.* Discovery and characterization of small molecules that target the GTPase Ral. *Nature* doi:10.1038/nature13713