Discovery and biological evaluation of PQR620, a highly potent and selective mTORC1/2 inhibitor

Denise Rageot[1], Florent Beaufils[2], Anna Melone[1], Thomas Bohnacker[1], Marc Lang[2], Jürgen Mestan[2], Vladimir Cmiljanovic[2], Petra Hillmann[2], Paul Hebeisen[2], Doriano Fabbro[2], Matthias P. Wymann[1]

[1]Department of Biomedicine, Mattenstrasse 28, University of Basel, 4058 Basel, Switzerland
[2]PIQUR Therapeutics AG, Hochbergerstrasse 60C, 4057 Basel, Switzerland

The mammalian target of rapamycin (mTOR) signaling pathway plays a fundamental role in cell proliferation, differentiation, growth and survival.[1] Drugs targeting the mTOR signaling pathway represent a valuable path to address cancer therapeutic strategies.[2] Here, we report the lead optimization of PQR620, a novel potent and selective brain penetrant inhibitor of mTORC1/2.

The development of selective mTOR inhibitors is particularly challenging due to extensively conserved amino acid residues in the ATP binding pocket of PI3K and PI3K-related protein kinases. Here, we present a detailed ligand-based structure activity relationship study allowing selective targeting of mTOR kinase activity. Systematic variation of the hinge region and affinity binding motifs led to the identification of PQR620. Substitution of the morpholine binding to the hinge region and introduction of a 2-aminopyridine, substituted with a difluoromethyl group, induced a >1000-fold selectivity towards mTOR over PI3Kα in enzymatic binding assays.

In A2058 melanoma cells PQR620 demonstrated inhibition of protein kinase B (PKB, pSer473) and ribosomal protein S6 (pS6, pSer235/236) phosphorylation with IC_{50} values of 0.2 µM and 0.1 µM, respectively. PQR620 showed excellent selectivity over a wide panel of kinases, as well as excellent selectivity *versus* unrelated receptor enzymes and ion channels. Moreover, PQR620 demonstrated potency in a panel of 66 cancer cell lines (NTRC Oncolines™) to prevent cancer cell growth ($^{10}\log(IC_{50}, nM) = 2.86$, corresponding to an IC_{50} of 723 nM). The physico-chemical properties of PQR620 result in good oral bioavailability and excellent brain penetration. In mice and rats oral application of PQR620 exhibited a dose-proportional PK. Plasma to brain ratio was at least 1 and C_{max} was reached after 30 minutes.

PQR620 shows anti-tumor effects *in vivo* and is currently in pre-clinical development.

[1] Laplante M., Sabatini D. M., *Cell* **2012**, *149*, 274-293.
[2] Guertin D. A., Sabatini D. M., *Cancer Cell* **2005**, 12, 9-22.