mTOR is a sensor of mitogen, energy and nutrient levels, a central controller of cell growth and a negative regulator of autophagy. The PI3K-AKT-mTOR pathway is one of the most frequently dysregulated pathways in human tumors. mTOR forms two distinct complexes mTORC1 and mTORC2, affecting p70S6K and 4EBP1 and pAKT, respectively. Inhibition of p70S6K by rapamycin relieves a negative feedback loop to IRS1 resulting in AKT activation. This is thought to limit the clinical activity of rapalogues in oncology.

AZD8055 is an ATP-competitive inhibitor of mTOR kinase, decreasing pS6K and p4EBP1 as well as pAKT on Ser473. AZD8055 decreases the phosphorylation of 4E-BP1 at position 37 and 46, phosphorylation resistant to rapamycin. This leads to a greater inhibition of cap-dependent translation compared to rapamycin.

In vitro, this dual target inhibition translates into a greater growth inhibitory effect than rapamycin and in some cases cell death. AZD8055 also induces autophagy in some cell lines. The inhibition of both mTORC1 and mTORC2 complexes in tumor bearing animals is observed at well-tolerated doses and results in a durable anti-tumor growth inhibition in several xenograft models. AZD8055 is currently in clinical development.