

MCF10A X-MAN[®] Cell Lines endogenously expressing mutant or wild-type PI3K: A model system for screening mTOR-targeted compounds

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Introduction

The PI3K pathway is aberrantly activated in numerous cancers, either through oncogenic activation of upstream effectors or through mutation of PI3K itself. The most common of these mutations is H1047R, which results in a constitutively active PI3K α that activates key downstream effectors, including mTOR. As a result of this, mTOR has emerged as an attractive drug target in cancers that exhibit aberrant PI3K pathway activation and a recent study has shown that inhibition of mTOR selectively slows the growth of PI3K α H1047R-expressing cells¹.

MCF10A parental and PI3K α (H1047R/+) paired cell lines have been generated using Horizon Discovery's proprietary technology. These cell lines are genetically identical except for the mutation status of the endogenous PI3K α gene, allowing the expression of mutant PI3K α to be directly studied at the endogenous level.

These isogenic lines have made it possible to test mTOR-targeted agents, such as everolimus, in a patient-relevant model system. By utilizing condition scouting, we found that low serum conditions were required for the phenotype of the driving mutation to become dominant. In this way we have been able to reveal a differential sensitivity of the wild type PI3K α (parental) and PI3K α (H1047R/+) lines to everolimus, an mTOR inhibitor, thus identifying potential patient populations that may benefit from these targeted agents.

Cell Lines Used

Cell Line	Genotype	Cat. No.
MCF10A	PI3K α (H1047R/+)	HD 101-011

Results and Discussion

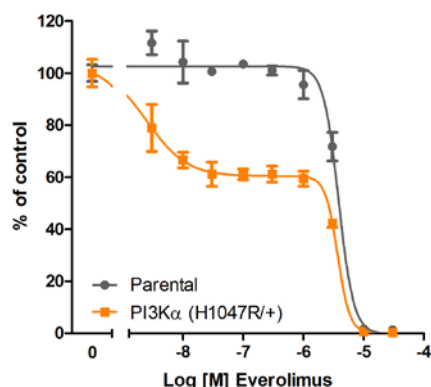


Figure 1. Low concentrations of everolimus selectively inhibit the growth of PI3K α H1047R-expressing cells. Isogenic MCF10A parental and PI3K α (H1047R/+) cells were seeded into low serum media and then treated with everolimus for 6 days.

MCF10A parental and PI3K α (H1047R/+) were tested in a proliferation assay with the mTOR inhibitor, everolimus. Using the MCF10A PI3K isogenic system, under specialist assay conditions it was possible to demonstrate that inhibition of mTOR selectively slows the growth of PI3K α H1047R-expressing cells.

Conclusion

X-MAN[®] Cell Lines, offer a way to interrogate the effect of mTOR inhibitors in a clean system without the caveats associated with protein over-expression studies and allow rational patient stratification without the need for large cell line panels.

Horizon Support

Horizon supplies genetically-defined cell lines, custom cell line generation, *in vivo* models, reporter gene assay kits, molecular reference standards and assay development and screening services to organizations engaged in academic research; drug discovery and development; clinical diagnostics; and biopharmaceutical process optimization. Please contact us to learn more about how Horizon can support your work.

Cell lines similar to those listed in this Application Note include:

Cell Line	Genotype	Cat. No.
MCF10A	PI3K α (E545K/+)	HD 101-002
MCF10A	PTEN (-/-)	HD 101-006
MCF10A	AKT1 (E17K/+)	HD 101-007
MCF10A	K-Ras (G12V/+)	HD 101-004
MCF10A	K-Ras (G12V/+); PI3K α (H1047R/+)	HD 201-002
MCF10A	K-Ras (G12V/+); PI3K α (E545K/+)	HD 201-003

References

1. Nicolantonio *et al.*, J Clin Invest. 2010 (120) p2858