United in science.

Synergizing *in vitro* and *in vivo* testing to predict drug sensitivity

Target therapies are aptly named. They specifically target cancer cells and largely leave normal cells alone, resulting in fewer patient side effects. These precision medicines attack cancer cells in many ways, including:

- Preventing proliferation
- Initiating apoptosis
- Preventing angiogenesis
- Triggering immune response

As no two cancers are identical, no two treatments should be either. We need to understand which targeted therapies will have the greatest efficacy on every single patient.

Leveraging the breakthroughs in next-generation sequencing technologies, we can now extract vital genomic data that reveals the unique mutations within a tumor. Armed with this knowledge, we can tailor a precise treatment regimen for each individual, optimizing their chances for successful outcomes.

This document details Charles River Laboratories' approach, combining *in vitro* and *in vivo* functional testing to determine prognostic impact of mutational status in Acute Myeloid Leukemia (AML) to predicting sensitivity against targeted therapy.

Featured scientist:

Bincy John, PhD
Research Scientist,
Charles River Laboratories

"To support our clients' oncology drug discovery programs and deepen our understanding of novel therapies, we utilize innovative *in vitro* and *in vivo* validation platforms. Here we utilized complementary approaches combining different *in vitro* and *in vivo* models to understand the impact of differential mutational status of molecular target fms-like tyrosine kinase 3 (FLT3) in Acute Myeloid Leukemia Models (AML). We identified the prognostic impact of FLT3 inhibitor Gilteritinib on the allelic ratio of FLT3 internal tandem duplications."

The Charles River Approach.

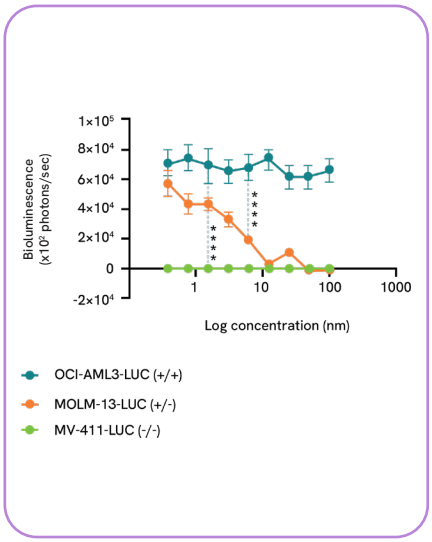
Principle

***In Vitro* Discovery** — ***In Vivo* Validation**

Assess potency against mutated cell lines → Probe signaling pathways for MOA → Determine survival benefit

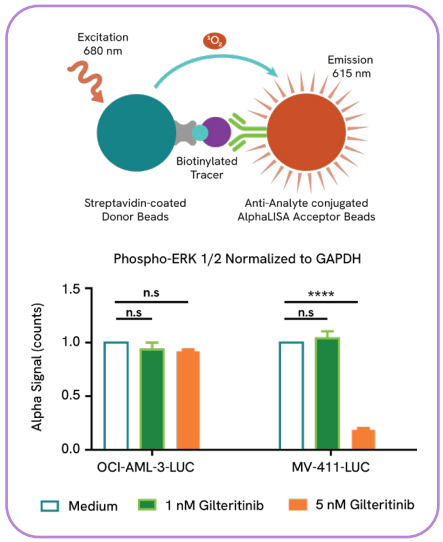
In practice

Charles River Demonstrates: Differential FLT3 mutational status in Acute Myeloid Leukemia predicts sensitivity to FLT3 inhibitor Gilteritinib *in vitro* and *in vivo*



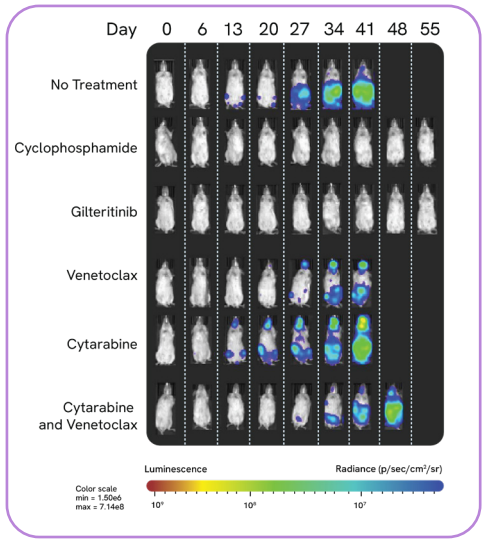
Cell viability

Gilteritinib is shown to induce cytotoxicity *in vitro* through dose dependant reduction of cell viability in FLT3-ITD mutated MV-411 AML tumor cell line



Signaling pathways

Gilteritinib mediates specific inactivation of FLT3 signalling shown by inhibition of p-ERK in AML cells harboring FLT3-ITD mutation



Disease progression

Highest therapeutic activity of Gilteritinib in FLT3 (-/-) MV-411 AML shown *in vivo*

Enabling technologies

Image based viability assessment — learn more

No-wash immunoassays — learn more

In vivo preclinical imaging solutions — learn more

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