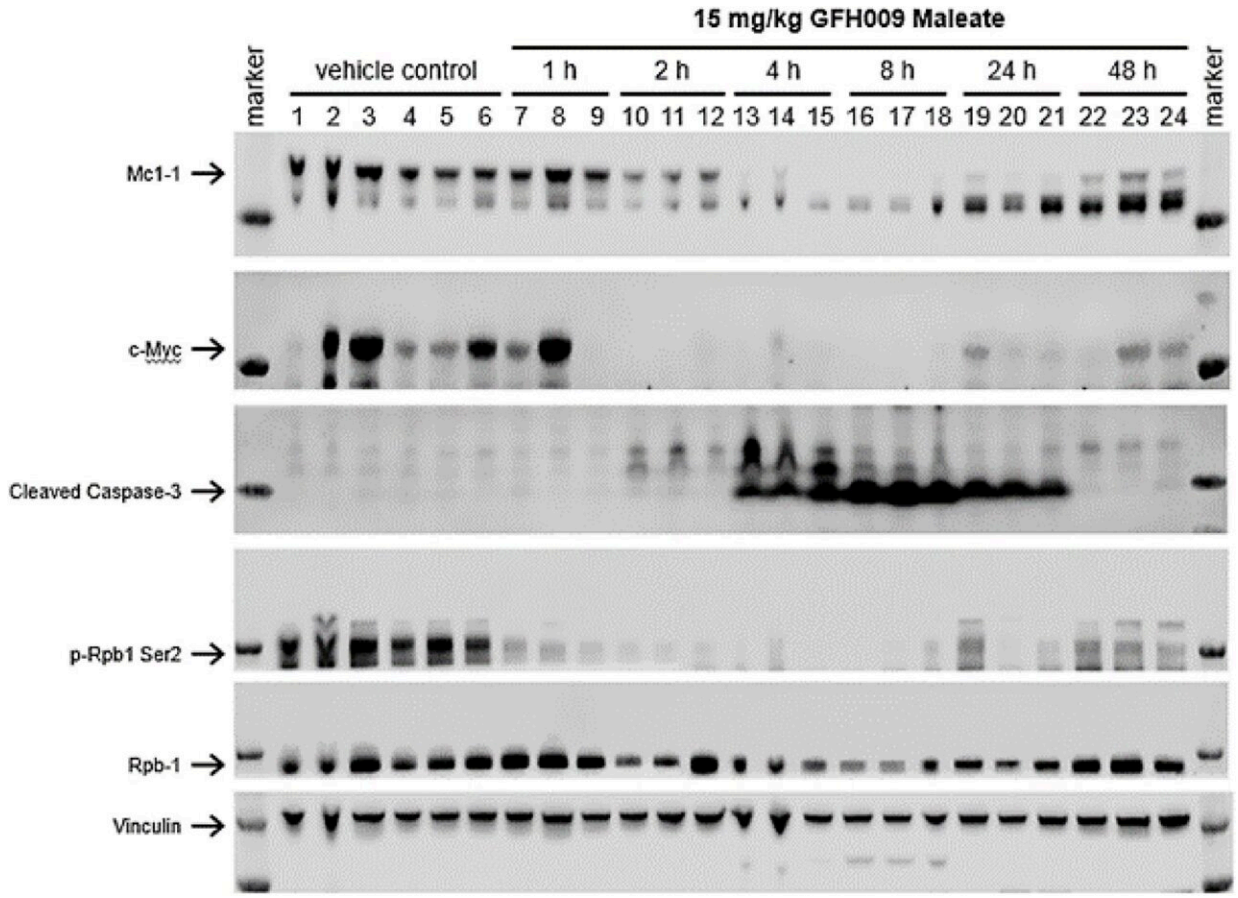
Potent and highly selective CDK9 inhibitor for treatment of hematologic malignancies

December 29 2023



Effect of GFH009 treatment on CDK9-dependent protein expression in vivo. Credit: 2023 Zhou et al

To evade cell cycle controls, malignant cells rely upon rapid expression

of select proteins to mitigate pro-apoptotic signals resulting from damage caused by both cancer treatments and unchecked over-proliferation. Cyclin-dependent kinase 9 (CDK9)-dependent signaling induces transcription of downstream oncogenes promoting tumor growth, especially in hyperproliferative "oncogene-addicted" cancers, such as human hematological malignancies (HHMs).

In a new study published in *Oncotarget* titled "The pharmacodynamic and mechanistic foundation for the antineoplastic effects of GFH009, a potent and highly selective CDK9 inhibitor for the treatment of hematologic malignancies," researchers from GenFleet Therapeutics Inc. and Sellas Life Sciences Group aimed to summarize current knowledge underlying the mechanism of action (MOA) of GFH009 and explain its robust anti-cancer activity.

"Understanding GFH009's MOA allows for a more optimal clinical development path, given the potential for meaningful benefits in patients with hematological malignancies," state the researchers.

GFH009, a potent, highly selective CDK9 small molecule inhibitor, demonstrated antiproliferative activity in assorted HHM-derived cell lines, inducing apoptosis at IC50 values below 0.2 μM in 7/10 lines tested. GFH009 inhibited tumor growth at all doses compared to controls and induced apoptosis in a dose-dependent manner.

Twice-weekly injections of GFH009 maleate at 10 mg/kg significantly prolonged the survival of MV-4-11 xenograft-bearing rodents, while their body weight remained stable. There was marked reduction of MCL-1 and c-MYC protein expression post-drug exposure both in vitro and in vivo. Through rapid 'on-off' CDK9 inhibition, GFH009 exerts a proapoptotic effect on HHM preclinical models triggered by dynamic deprivation of crucial cell survival signals.

"Our results mechanistically establish CDK9 as a targetable vulnerability in assorted HHMs and, along with the previously shown superior class kinome selectivity of GFH009 vs. other CDK9 inhibitors, strongly support the rationale for currently ongoing clinical studies with this agent in acute myeloid leukemia and other HHMs," claim the researchers.

More information: Fusheng Zhou et al, The pharmacodynamic and mechanistic foundation for the antineoplastic effects of GFH009, a potent and highly selective CDK9 inhibitor for the treatment of hematologic malignancies, *Oncotarget* (2023). DOI: 10.18632/oncotarget.28543