Discovery of small molecule Gαq/11 protein inhibitors against uveal melanoma

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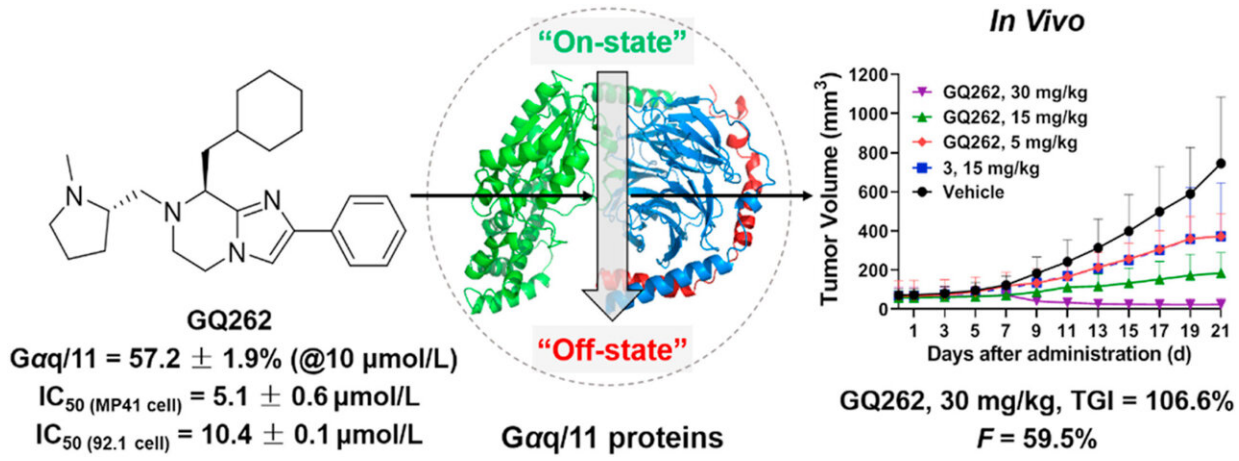

Graphical abstract:Constitutively activated Gαq/11 proteins drive the vast majority of uveal melanoma (UM). GQ262 effectively combats UM both in vitro and in vivo by targeting Gαq/11 directly. Credit: Acta Pharmaceutica Sinica B (2022). DOI: 10.1016/j.apsb.2022.04.016

Constitutively activated G proteins caused by specific mutations mediate the development of multiple malignancies. The mutated Gαq/11 are perceived as oncogenic drivers in the vast majority of uveal melanoma (UM) cases, making directly targeting Gαq/11 to be a promising strategy for combating UM.

In this article, the authors report the optimization of imidazopiperazine

derivatives as Gαq/11 inhibitors and identified GQ262 with improved Gαq/11 inhibitory activity and drug-like properties. GQ262 efficiently blocked UM cell proliferation and migration in vitro. Analysis of the apoptosis-related proteins, extracellular signal-regulated kinase (ERK), and yes-associated protein (YAP) demonstrated that GQ262 distinctly induced UM cells apoptosis and disrupted the downstream effectors by targeting Gαq/11 directly. Significantly, GQ262 showed outstanding antitumor efficacy in vivo with good safety at the testing dose.

These findings along with the favorable pharmacokinetics of GQ262 suggest that directly targeting Gαq/11 may be an efficient strategy against uveal melanoma.

The research was published in *Acta Pharmaceutica Sinica B*.

More information: Yang Ge et al, Discovery of small molecule Gαq/11 protein inhibitors against uveal melanoma, *Acta Pharmaceutica Sinica B* (2022). DOI: 10.1016/j.apsb.2022.04.016

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