Washington University in St. Louis
Office of Technology Management

SMALL MOLECULE INHIBITORS OF G PROTEIN ACTIVITY TO TREAT UVEAL MELANOMA, AND OTHER CANCERS AND DISORDERS

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Disease indication – Uveal melanoma and other G protein-driven disorders, including other cancers (certain vascular tumors, colon, lung, adenocarcinoma, skin melanoma, thyroid adenoma), cholera and Sturge-Weber Syndrome

Drug format – small molecule (FR900359, a bioavailable inhibitor of G protein activation, and its derivatives/analogs)

Drug class – first-in-class

Research stage and Preliminary data:

- *In vitro*:
  - FR900359 ("FR") targets human uveal melanoma cells by arresting growth, inducing apoptosis, and reverting a subset of those cells to a pre-cancerous state
  - effects of FR on tumor cells are specific for oncogenic $G\alpha_{q/11}$
- *In vivo:* FR arrests uveal melanoma tumor growth in mouse models
- *Medicinal chemistry:* the inventors are using rational design to create next generation compounds/derivatives

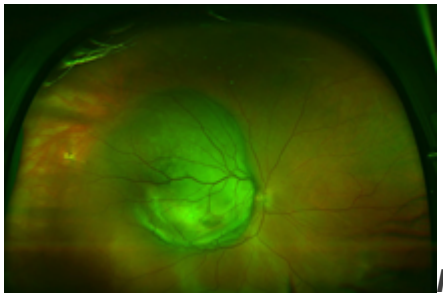

***Figure**: Uveal melanoma, the large green mass pictured, is an aggressive and deadly cancer that originates in the eye and metastasizes often to the liver. Treatment of primary uveal melanoma tumors fails to improve the prognosis for metastatic disease. Effective therapy for metastatic uveal melanoma is lacking.*

Target – G protein alpha-subunits of the Gq (GNAQ) and G11 (GNA11) class; potential for derivative molecules to target other G protein subtypes in a variety of diseases

Background:

Uveal (ocular) melanoma (UM) is a highly aggressive cancer in which half of patients develop metastases that respond insignificantly to all current therapeutic modalities, including cytotoxic

chemotherapeutics, radiation and immune checkpoint inhibitors. The mean survival of patients with metastatic UM is less than 12 months. More than 90% of UM tumors are driven by mutations that cause $G\alpha_q$ or $G\alpha_{11}$ to be constitutively active, thereby triggering signaling cascades that drive tumorigenesis. Attempts to treat UM by inhibiting signaling downstream of Gαq or Gα11 thus far have failed in clinical trials.

Mutant constitutively active Gq causes Sturge-Weber syndrome and occurs in several other types of cancer, and constitutive activation of another G protein (Gαs) causes cholera.

Keywords – uveal melanoma, melanoma, G protein signaling, GNAQ (G Protein Subunit Alpha Q), GNA11 (G Protein Subunit Alpha 11), cancer, cholera, Sturge-Weber

Mode of action:

The inventors have demonstrated that FR directly inhibits mutant constitutively active $G\alpha_{q/11}$ in vitro and in vivo with high potency and efficacy. FR traps oncogenic $G\alpha_{q/11}$ in the inactive state by inhibiting GDP/GTP exchange, thereby shutting down all downstream signaling to inhibit UM cell proliferation and trigger apoptosis or re-differentiation into pre-cancerous cells. FR does not affect proliferation, survival or differentiation of UM cells driven by mutations in the BRAF gene (typical in skin melanoma).

Competitive edge:

- **Targeted therapy:**
  - first-in-class treatment to directly inhibit the oncogenic G protein that drives the vast majority of uveal melanoma tumors.
  - highly potent and specific for $G\alpha_{q/11}$, since FR has no effect uveal melanoma driven by BRAF.
- **Reverses tumor cells**
  - potential treatment for both primary and metastatic tumors
  - may slow conversion from indolent state to aggressive tumor
  - turns off Gq/11-driven signaling networks in vitro to inhibit tumor cell growth and survival, and force tumor cells to re-differentiate into pre-cancerous cells.
- **Potent –** potent (nM) and bioavailable small molecule
- **Local delivery –** for uveal melanoma treatment, FR can be delivered by injection into the eye or focal perfusion of the liver to avoid systemic side effects on healthy tissue.

Patent status – Targeted pharmacological therapeutics in uveal melanoma (PCT application, Publication No. WO2019060781A1)

Publications

- Onken, M. D., Makepeace, C. M., Kaltenbronn, K. M., Kanai, S. M., Todd, T. D., Wang, S., ... & Blumer, K. J. (2018). Targeting nucleotide exchange to inhibit constitutively active G protein α subunits in cancer cells. *Sci. Signal.*, 11(546), eaao6852.
- Scientists identify weak point in deadly eye melanoma, *theSOURCE*, Sept. 4, 2018.

Web Links

- Blumer Lab