

Potential Chemotherapeutic Agents for the Treatment of NF2-associated Schwannoma and Meningioma



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Using various cell culture and animals models to test effective drug treatments for NF2-associated tumors, we previously reported that AR-42 (formerly named OSU-HDAC-42), a pan-histone deacetylase (HDAC) inhibitor, potently inhibited the growth of schwannomas and meningiomas.

We further investigated the molecular mechanism underlying AR-42-mediated growth arrest in these tumor cells. A human Phase I clinical trial for AR-42 in advanced or recurrent solid tumors, including vestibular schwannomas and meningiomas, has been initiated at The Ohio State University.

In addition, we have tested six additional small-molecule inhibitors, including MK-2206 (an AKT inhibitor), three Aurora kinase inhibitors (PF-03814735, MLN8237, and VX-680), ICG-001 (an inhibitor of Wnt/ β -catenin signaling), and JNJ-26481585 (a pan-HDAC inhibitor). We found that the HDAC inhibitor, JNJ-26481585, efficiently inhibited proliferation of schwannoma and meningioma cells with the IC_{50} (50% inhibitory concentration) values of ~40-50 nanomolars. The three Aurora kinase inhibitors also suppressed schwannoma cell growth at sub-micromolars of concentration. The Wnt/ β -catenin signaling inhibitor, ICG-001, moderately reduced tumor cell proliferation, while the AKT inhibitor, MK-2206, was not effective.

Another approach to identify novel medical therapies that we have undertaken is to screen a library of pure, structurally defined natural compounds for potent growth inhibitory activity in schwannomas and meningiomas.

Previously, we identified several natural compounds that effectively reduced schwannoma and meningioma growth, including silvestrol, a rocaglate derivative from the tropical Asian plant *Aglaiia foveolata*. We also found that silvestrol induced cell cycle arrest at G2 phase in schwannoma and meningioma cells.

In addition, we investigated antitumor effects of two other plant-derived natural compounds, cucurbitacin D and goyazensolide, in schwannoma and meningioma cells. We found that cucurbitacin D inhibited proliferation of schwannoma and meningioma cells at sub-micromolars of concentration. Goyazensolide also suppressed schwannoma and meningioma growth at about 1 micromolar of IC_{50} . Both cucurbitacin and goyazensolide induced G2 arrest in NF2-deficient meningioma cells. Presently, we are investigating the growth-inhibitor mechanisms of drug action of these compounds.

Q&A

- 1) **Advocure: What are the next anticipated steps with your studies? With AR-42, how long will it be before the phase 1 trials show measurable results?**

Welling: The clinical trial of AR-42 that is ongoing in Dr. Welling's clinic at The OSU Eye and Ear Institute is a Phase 1/2b clinical trial. The study is designed to recruit 20 patients with NF2-related vestibular schwannoma, sporadic vestibular schwannoma, NF2-related meningiomas, and/or sporadic meningiomas. The primary objective is to determine whether AR-42 hits the targets (e.g., AKT kinase and cell cycle regulators). The secondary objectives include (1) assessment of any audiometric changes pre- and post AR-42 administration, (2) evaluation of any volumetric tumor reduction after 10 doses of AR-42, (3) further assessment of the biological effects of AR-42 on the AKT pathway, tumor cell proliferation, cell cycle, cell death, and angiogenesis, (4) exploration of a potential biomarker, (5) the status of the NF2/Merlin and treatment, and (6) determination of the steady-state plasma and intra-tumoral concentrations of AR-42. The study is planned for three years.

- 2) **Advocure: With Silvestrol, at what point could that be recommended, if ever, as a supplement worth taking?**

Welling: In our cell culture study, silvestrol potently inhibited proliferation of both NF2-deficient schwannoma and meningioma cells. Our OSU collaborator (Dr. A. Douglas Kinghorn) have shown anti-tumor efficacy of silvestrol in multiple cancer models, including ALL. Silvestrol is presently under preclinical development by the NCI. Dr. Kinghorn has been able to obtain sufficient quantity for us to study of the in vivo effects of silvestrol in animal models of schwannoma and meningioma. Also, the toxicity and tolerability profile of silvestrol is being evaluated at OSU. After all these studies are completed, we may be able to assess whether silvestrol is beneficial as a supplement.