Washington University in St. Louis
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TUMOR TREATMENT FOR PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 (NF1)

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Technology Description

Scientists at the Washington University Neurofibromatosis Center have developed a patented, first-in-class method for treating neurofibromatosis type 1 (NF1) with small molecule inhibitors of targets in the mTOR (mammalian target of rapamycin) signaling pathway. NF1 is a relatively common genetic condition that predisposes patients to cancerous tumors, such as optic gliomas, neurofibromas, and malignant peripheral nerve sheath tumors (MPNSTs), the latter of which are associated with a poor overall prognosis. Current therapies for these tumors typically rely on drugs used for sporadic cancer, leaving an unmet need for more effective treatment targeted specifically to NF1.

This new NF1 treatment relies on the finding that two components in the mTOR pathway, nucleophosmin (NPM) and Rac1, are specifically affected by the loss of neurofibromin (the *NF1* gene product), leading to cellular changes that ultimately result in neoplastic transformation. Therefore, NPM or Rac1 inhibitors could be used as a specific, novel treatment for NF1. The inventors have also identified several molecules that inhibit these targets, which could potentially lead to improved treatments for these deadly cancers.

Stage of Research

- **Validation/mechanism of action** – Using cell models of NF1 (*Nf1*-deficient primary astrocytes and MPNST cells), the inventors validated and characterized the role of the mTOR pathway (including Rac1 and nucleophosmin) as a downstream target of neurofibromin. This pathway regulates actin cytoskeleton dynamics and cell proliferation in astrocytes, suggesting that targeting these signaling intermediates may be useful for treating NF1.
- **Drug candidates** – The inventors have identified one compound that can inhibit nucleophosmin and two that inhibit Rac1 to rescue the cells from the effects of *Nf1* loss.

Applications

- **Therapeutic for neurofibromatosis**

Key Advantages

- **First-in-class:**
  - current therapies for patients with NF1 typically rely on drugs used for sporadic cancer
  - method of treatment relies on inhibiting nucleophosmin (NPM) or Rac1, novel targets for NF1-specific treatment
- **Unmet medical need -** currently there is no treatment on the market for NF1

Publications

- **Sandsmark, D. K., Zhang, H., Hegedus, B., Pelletier, C. L., Weber, J. D., & Gutmann, D. H. (2007).** Nucleophosmin mediates mammalian target of Rapamycin–Dependent actin cytoskeleton dynamics and proliferation in neurofibromin-deficient astrocytes**.** *Cancer Research*, 67(10), 4790-4799.

Patents

- Neurofibromin pathway modulators (U.S. Patent No. 8101606)

Websites

- Washington University Neurofibromatosis (NF) Center
- Weber Lab
- Gutmann Lab