**NRF2 Inhibitors as Cancer Therapeutics**

**Technology Description**

NRF2, a transcription factor involved in the cellular response to oxidative stress, appears to play a role in the metabolic reprogramming of cancer cells. Cells with constitutive NRF2 activation show increased resistance to both chemotherapy and radiotherapy. The anti-parasitic drug pyrimethamine has been shown to inhibit NRF2, but no version of an NRF2 inhibitor has been approved for use in cancer.

These small molecules are analogs of the known NRF2 inhibitor pyrimethamine. Constitutive activation of NRF2 promotes metabolic reprogramming, leading to cancer cell proliferation, chemoresistance, and radio-resistance.

**Stage of Research**

The researchers have synthesized a series of pyrimethamine analogs and tested their ability to inhibit NRF2. The lead compound, WCDD104, provides 10x more inhibition of NRF2 than pyrimethamine, and

WCDD115 is 30x more potent. Research is ongoing to better optimize the lead compound and to test the analogs *in vivo*.

**Applications**

Treating diseases related to oxidative stress, including:

* Cancer
* Autoimmune disease
* *Toxoplasma* infection

**Key Advantages**

* Though pyrimethamine is FDA-approved, there are currently no NRF2 inhibitors approved for use in cancer.
* The lead analog is 10x more effective at inhibiting NRF2 than pyrimethamine.