

## NRF2 INHIBITORS AS CANCER THERAPEUTICS

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**Disease indication** – Diseases related to oxidative stress, including cancer, autoimmune disease, and *Toxoplasma* infection

**Drug format** – Small molecule

**Drug class** – Best-in-class

**Research stage and preliminary data** – 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 *in vivo*.

**Target** – NRF2 transcription factor

**Background** – 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.

**Mode of action** – These molecules are analogs of known NRF2 inhibitor pyrimethamine. Constitutive activation of NRF2 promotes metabolic reprogramming, leading to cancer cell proliferation and chemo-/radioresistance.

**Competitive edge** – 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.

**Publication** – Cloer EW, Goldfarb D, Schrank TP, Weissman BE, Major MB. (2019). NRF2 activation in cancer: from DNA to protein. Cancer Research, 79(5): 889-898.

Patent status - Pending

Web Links – Major Profile & Lab; Dolle Profile