

A017 A Novel Orally Available Wnt-Pathway Inhibitor for the Treatment of Metastatic Cancers

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Introduction: We have developed a novel drug compound (OBD9) which blocks growth of metastatic cancer cells both *in vitro* and *in vivo*. We now identify OBD9 as an effective Wnt-signaling inhibitor targeting TNIK (TRAF2 And NCK Interacting Kinase) and we hypothesize that OBD9 represent a novel therapeutic option for patients with tumors that have an activated Wnt signaling pathway. **Methods:** To find novel drug candidates that selectively inhibit metastatic tumor cell viability, a drug screen was firstly performed and results of the screen identified members of the FDA-approved benzimidazole methylcarbamate family (e.g. mebendazole (MBZ) and albendazole (ALB)) as potential therapies for metastatic cancer. Earlier work also supports a role for this chemical family in the potential treatment of multiple cancers, but progress has been stalled by their poor water solubility and poor bioavailability for systemic delivery to disseminated tumors. We therefore synthesized a novel compound (OBD9) containing the scaffold of MBZ coupled to an oxetane group to enhance aqueous solubility to 361 μ M. OBD9 demonstrates significant cytotoxicity toward a variety of cancer cell types including colon, lung, and prostate cancers (IC₅₀: 0.9-2 μ M). In a mouse xenograft model using highly aggressive PCMLN4 prostate cancer cells, OBD9 at 30 mg/kg significantly repressed growth of established tumors with no visible toxicity. In a mouse xenograft model of human A549 lung cancer cell line, orally delivered OBD9 also dramatically inhibited the growth of established tumors at 30 or 90 μ M without noticeable toxicity. **Results:** Mechanistically, we find that OBD9 treatment significantly reduces TNIK levels as early as 4 hours via an autophagy-dependent protein degradation pathway. TNIK functions as an activator of Wnt signaling pathway via phosphorylation of the beta-catenin/TCF4 complex that regulates Wnt downstream targets. We show that OBD9 treatment inhibits colon cancer cell growth and both qPCR and Western blot data suggest that Wnt signaling downstream targets, such as TCF4, AXIN2 and cMyc, are all significantly suppressed by OBD9 via the inhibition of TNIK. **Conclusions:** Overall, our *in vitro* and *in vivo* data suggest that OBD9 potentially represents a novel therapeutic option for multiple cancers including but not limit to colon, lung and prostate cancer.