ET-24. A NOVEL TROJAN HORSE FOR IN-VIVO SENSITIVITY TESTING OF MEDULLOBLASTOMA THERAPIES

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INTRODUCTION: Neural tumors such as medulloblastomas, have distinct genetic signatures, including neurotransmitter receptors, indicative of their developmental lineage. Neurotransmitter receptors have been well-defined in normal neurophysiological, developmental, and pharmacological settings. However, their importance in the maintenance and progression of brain tumors and, importantly, the effect of their targeting in brain cancers remains unclear. In a recent genomic study of primary medulloblastomas, high levels of GABRA5 expression were observed in a particularly aggressive molecular subtype of medulloblastoma (MYC-amplified). We then went on to demonstrate that modulation of GABRA5 receptor activity in these tumors could alter their survival characteristics and provide a novel treatment strategy for individuals diagnosed with this subtype of medulloblastoma. Using a novel implantable device for high-throughput in-vivo drug sensitivity measurements we performed the first in-vivo efficacy studies of several lead compounds. These lead compounds will be further developed to reduce their potential toxicity and side-effects. METHODS: We used an implantable device to treat flank medulloblastoma tumors expressing GABRA5 in vivo with local microdoses of cisplatin and GABA receptor agonists, such as diazepam, QHii066, and other similar derivatives. We compared these to non-GABRA5 expressing tumors. Our results revealed significantly higher apoptosis induction by these compounds in GABRA5 expressing flank tumors with the GABA receptor agonists, whereas we do not see a similar effect with Cisplatin. The converse is true for the non-GABRA5 expressing tumors. CONCLUSION: This is the first successful in-vivo study demonstrating that tumors expressing GABRA5 are sensitive to GABRA5 agonists, providing a more efficient and potentially less toxic approach to developing GABRA5 agonists and other compounds. Validation of targets and identification of the most active lead compounds in vivo before pharmacological optimization may represent a new paradigm for developing drugs more efficiently in whole animal or human studies in the future.

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