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7. Category:RecordsDespite numerous advances in the treatment of many childhood cancers, gliomas are among the most lethal of all cancers, and the majority of children with brain tumors die of their disease. As a major reason for this malignant effectiveness, gliomas are highly resistant to chemotherapy and radiation. Specific Aim 1 is designed to determine the role of lysosomal protease inhibitors in the sensitivity of glioma cells to proteasome inhibition. Aim 2 will determine the efficacy of selective apoptosis-inducing TRAIL in glioma therapy. TRAIL selectively kills glioma cells both in culture and in mice. Studies of TRAIL resistance in gliomas will identify new pathways for glioma treatment and allow the development of glioma resistance to TRAIL-based therapy. Specific Aim 3 will determine the role of HIF1, the regulatory protein for the hypoxia-inducible pathway, in modulating glioma cell metabolism and chemoresistance. Hypoxia-inducible factor 1, more commonly known as HIF1, is a transcription factor that regulates gene expression in response to low oxygen levels. In normoxic conditions, HIF1 is a protein complexed with the p300 corepressor and is rapidly degraded. The hypoxia-inducible pathway is another key signaling pathway involved in cell survival in the face of low oxygen levels. Studies on HIF1 activation in glioma cells will lead to a better understanding of the regulation of HIF1 in the hypoxia-inducible pathway. Successful completion of these studies will help the understanding of the pathogenesis of gliomas and may ultimately lead to the development of better treatment strategies for this deadly disease. PUBLIC HEALTH RELEVANCE: Children with brain tumors, such as glioma, are among the most vulnerable patient populations. Despite advances in the treatment of many childhood cancers, gliomas are among the most lethal of all cancers, and the majority of children with brain tumors die of their disease. As a major reason for this malignant effectiveness, gliomas are highly resistant to chemotherapy and radiation. This project is designed to determine the role of lysosomal protease inhibitors in the sensitivity of glioma cells to proteasome inhibition. Successful completion of these studies will help the understanding of the pathogenesis of gliomas and may ultimately lead to the development of better treatment strategies for this deadly disease.Reduction of secondary diseases in patients 1cb139a0ed

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