

SUMMARY

Malignant gliomas are characterized by infiltrative growth that causes progressive neurologic dysfunction and, almost invariably, death. Glioblastoma multiforme, the most common and aggressive form of glioma, typically recurs despite surgery, radiotherapy, and conventional chemotherapy. Oncolytic adenoviruses are promising therapies for the treatment of gliomas. **We have previously developed an oncolytic adenovirus Delta-24-RGD that is being tested by NCI/FDA for its use as anti-glioma agent in a Phase I clinical trial.** In this proposal, we aim to test the anti-cancer effect of ICOVIR *in vitro* and *in vivo*. *In vitro* preliminary data showed the ability of the endogenous E2F1 to bind the E2F1-responsible elements in ICOVIR resulting in an Rb-dependent replication phenotype. These results were also observed *in vivo* using a glioma xenograft model. Of importance, a pilot study showed that the administration of ICOVIR *in vivo* lead to a significant increase in the median survival of glioma-bearing mice and the generation of long-term survivors. Importantly, combination of ICOVIR with temozolomide and RAD001 resulted in a drastic improvement in tumor suppression and animal survival. Importantly, we have never observed similar results in our animal model using different combinations of chemotherapy, radiotherapy, gene therapy, and small molecules, **We believe that our pre-clinical data showing the *in vivo* anti-glioma effect of the combination of RAD001 and ICOVIR may constitute a breakthrough in the development of anti-glioma therapy** and should propel the further development of ICOVIR into the clinical setting.