Possible Cancer Treatment Using the *Drosophila* Glioma Model

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Abstract

Glioma is a deadly brain cancer, and current treatments have been unsuccessful in prolonging life more than a few months. In an effort to discover better treatments with more direct targets, we are conducting a chemical screen using Tyrosine Kinase inhibitors (Selleck Biochem). Promising results of such inhibitors will suppress the progression of glioma by (a) inhibiting the underlying molecular pathways activated in glioma, or (b) prevent rapid proliferation of the glia and other cells that encompass the glioma tumor. We have induced glioma in *Drosophila* by activating two of the most common oncogenic pathways, PI3K and Ras/MAPK. The activation of these pathways results in an enlarged brain from an increase in stem cells and their glia and neural progeny. These tumors cause the larvae to enter a prolonged larval phase, and eventually kill the organism. During our screen, larvae are added to food in their early third instar phase (72h old). The food is infused with 10 or 300uM chemicals in DMSO and where we then see effects on glioma growth, and survival in mature third instar stage (120h old). Using these metrics, here we present data from our screen on promising drugs from this academic year's testing focusing on drugs E7, E9, and E11. Once we identify potential glioma inhibitors in the primary screens, we will validate them in secondary screens.

Introduction

The goal of this experiment is to determine the limit of growth and progression of glioma after being treated with recently approved drugs that target Tyrosine kinases. The pathway used for the limit of the growth and progression of glioma are the Ras/MAPK and PI3K pathways in the model organism, *Drosophila Melanogaster.* The most frequent oncogenic mutation in most tumors, along with glioma is Ras^{V12}**.** When Ras^{V12} is activated, the result is cell proliferation and tumor invasions.

The PI3K pathway, a growth regulatory pathway that's responsive to growth factors, is also known to be responsive to many tumor suppressor genes apart of the same pathway. Pten is one of those tumor suppressor genes and it results in negative regulation of the PI3K pathway. We expressed $Pten^{RNAi}$ with activated Ras^{V12} to successfully model glioma in fly brains, since Pten mutations are found in patients' biopsies of glioma.

In this chemical screen, we tested the effectiveness of chemicals, more specifically the effectiveness of chemicals E7, E8, E11. The effectiveness is examined by dissecting the brain, along with imaging larvae brains and checking the survival rates of the larvae. We present our results on the inhibitors effect on glioma growth and the evidence for the overall effectiveness of this screen on the model organism.

Drug Screen Process

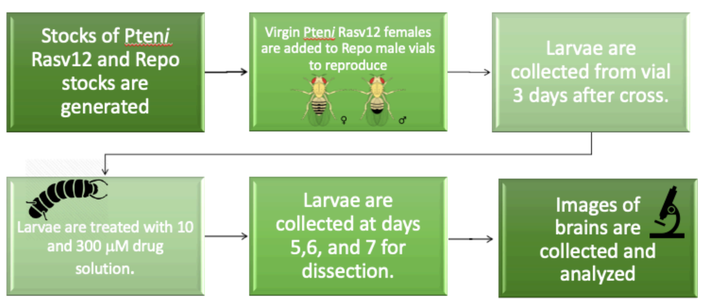
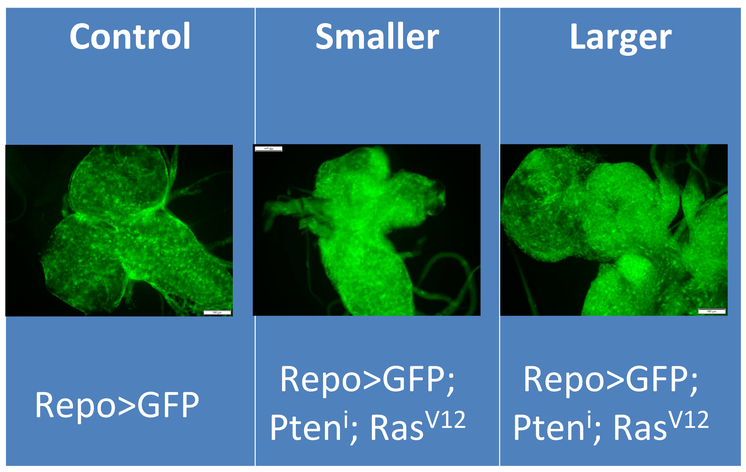


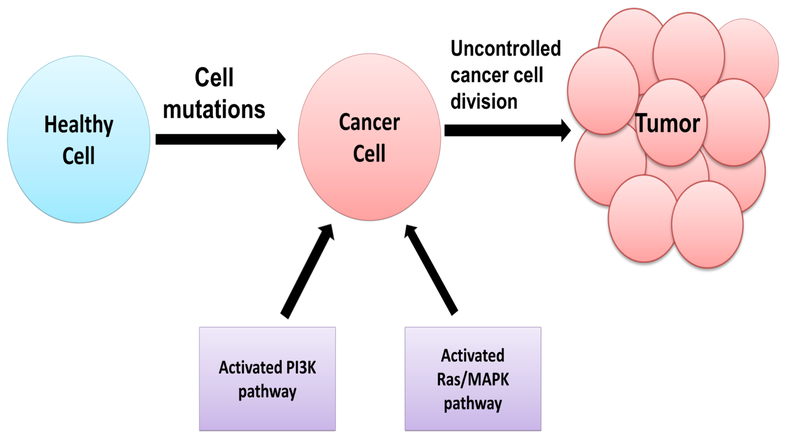
Table 1: Drug Data Summary

	10um	300um
E7 Drugs	In Progress.	**Showed slight Reduction.**
E9 Drugs	**No visual change in glioma size**	In Progress.
E11 Drugs	**Showed overall suppression**	In Progress.

Scales Used for Comparison

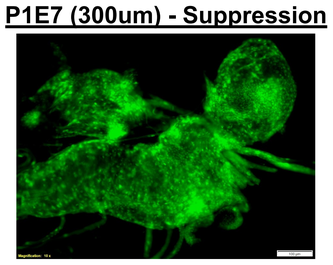


Glioma Progression

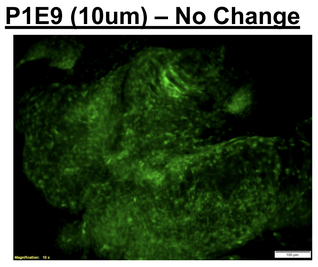


Overview of Enhancers & Suppressors

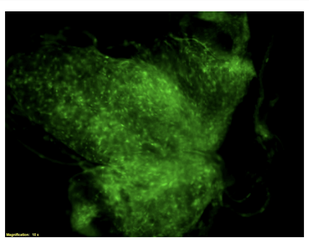
P1E7 (300um) - Suppression



P1E9 (10um) – No Change



P1E11 (10um) – Suppression



Conclusions

- The present drug screen examined potential tumor suppressing effects of tyrosine kinase inhibitors from a chemical library tested in a *Drosophila* model of glioma.
- Through our drug screen, we have tested drugs A-H in the chemical library. We have focused the present poster on P1E7, P1E9, and P1E11. Through our current results, we found that chemicals P1E7 and P1E11 both had tumor suppressing effects, at 300 uM and 10 uM respectively.
- The chemical P1E9 demonstrated no change in glioma size.
- Since both P1E7 and P1E11 demonstrated glioma inhibition, we plan to further validate these findings by performing secondary screens.
- In the future, we will continue analyzing other drugs from the chemical library in order to determine which chemicals are most effective in inhibiting glioma growth, as well as their optimal concentrations.

Future Directions

1. We plan to continue the chemical screen using additional drugs from the Selleck Biochem Chemical library.
2. We will begin to validate the potential glioma reducers to find the specificity and efficacy of these potential modifiers of glioma growth.

Acknowledgement

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