



Finding Glioma Growth Inhibitors using *Drosophila* models

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University
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Goals

1. Perform a chemical screen to find drugs that reduce the volume/growth of tumors
2. Safer and more effective way to combat cancer
3. Understand the biological pathways and their effect on *Drosophila* models



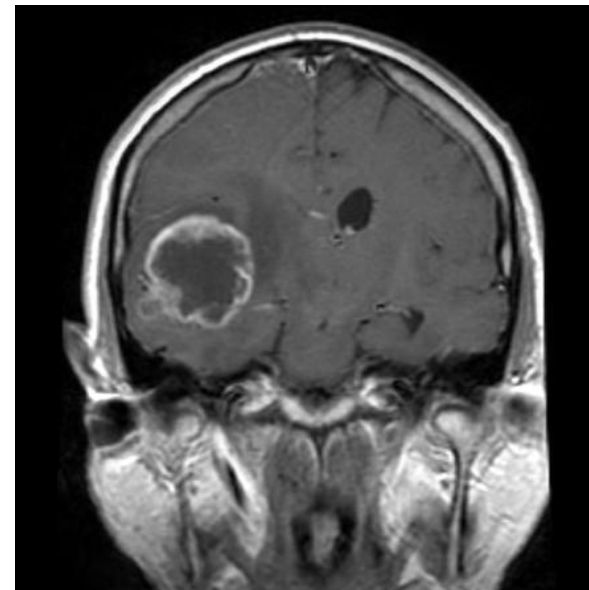
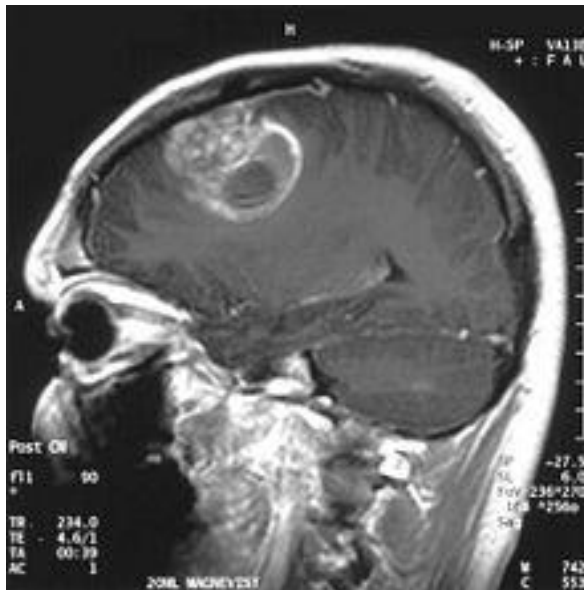
Agenda

- Background Information
- Drug Screen Process
- Results
- Conclusion



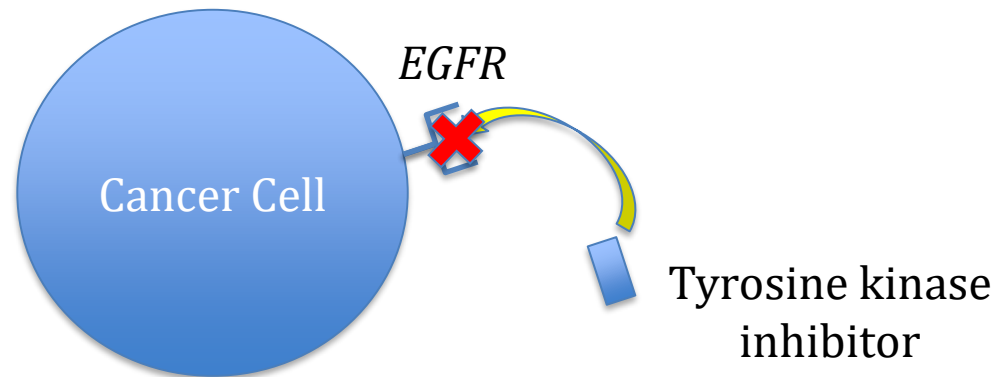
Background Information

- Glioblastoma multiforme
 - Most malignant form of the highest-grade glioma
 - Poor prognosis



Tyrosine Kinase Inhibitors

- Tyrosine kinase inhibitors
 - Blocks function of epidermal growth factor receptor (*EGFR*)
- *EGFR*
 - Serves as an “antenna,” receiving signals from other cells and the environment that tell the cell to grow and divide
 - Larger amount on surface of cancer cells



Experimental Model

- *Drosophila melanogaster* model
 - Has been shown to accurately demonstrate human glioma growth
 - Shares 70 percent of disease genes with humans; including 2 most frequent oncogenic pathways
 - Ras/MAPK: Oncogenic mutation
 - Pi3K: Growth regulatory



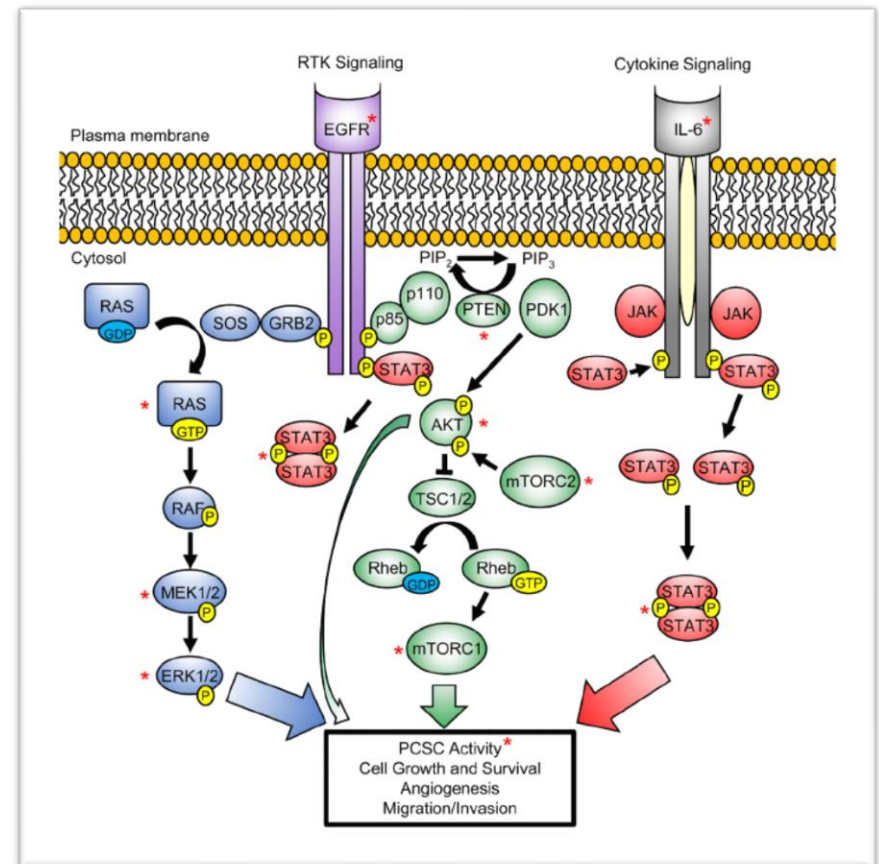
Experimental Model

- *Drosophila melanogaster* model
 - Two types of flies:
 - $Pten^{RNAi}, ras^{v12}$
 - $Pten^{RNAi}$ works to shut off a tumor-suppressor gene (*Pten*)
 - ras^{v12} works to promote tumor growth
 - *Repo GFP*
 - *Repo* works to drive the tumor progression, cancer growth cannot progress without it
 - *GFP* allows the glia cells in the brain to fluoresce under UV light

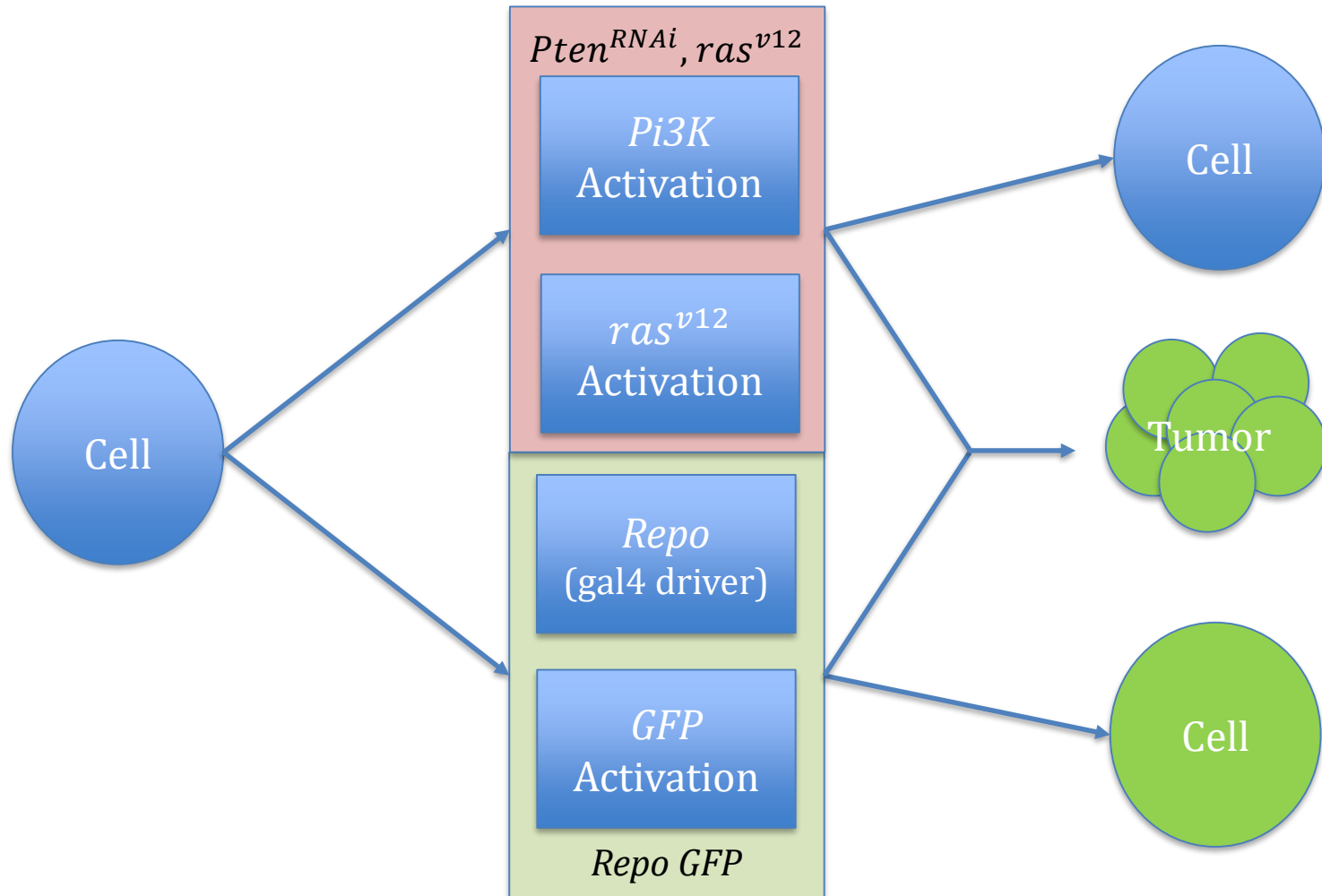


What are Pathways?

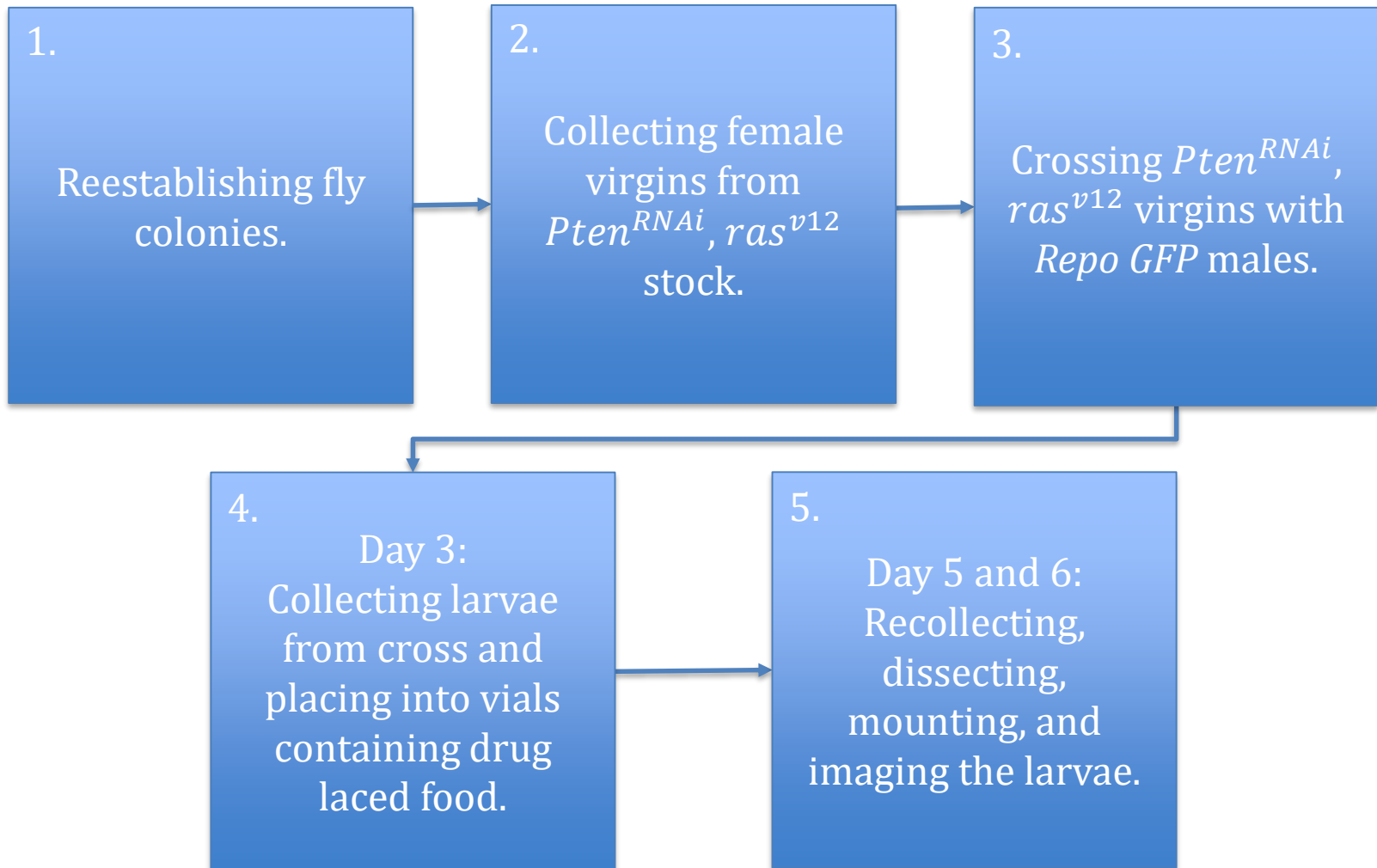
- Definition:
 - A series of actions among molecules within a cell that causes a certain change within that cell
 - Gene-regulation Pathway



Cancer Progression



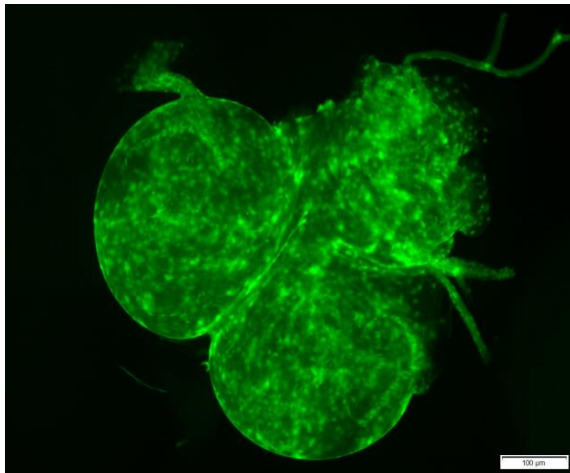
Drug Screen Process



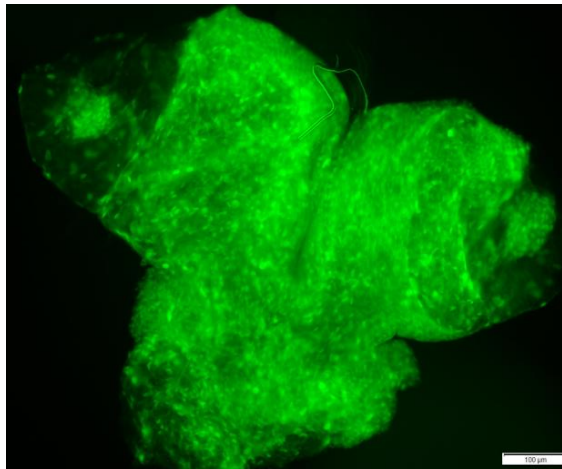
Results

- P1G8

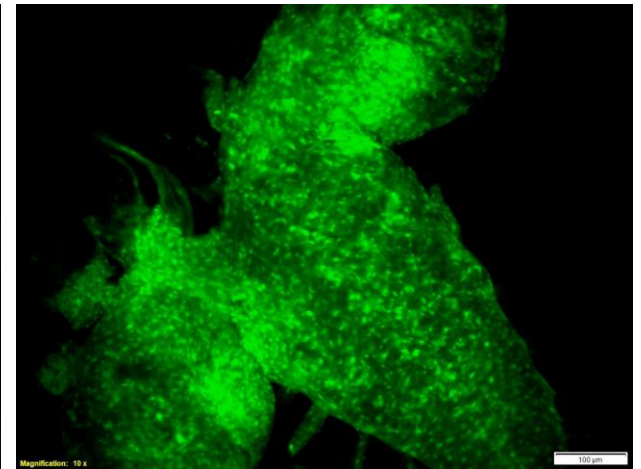
Repo control brain



Glioma brain



Our screen: 300 μM



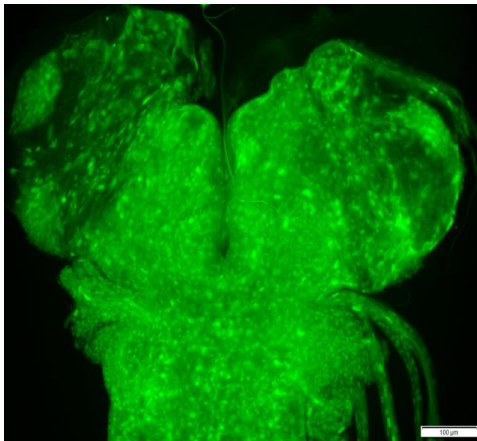
	Initial # of Larvae	Total # of Larvae
Cross	12	3
Cross (2)	13	0



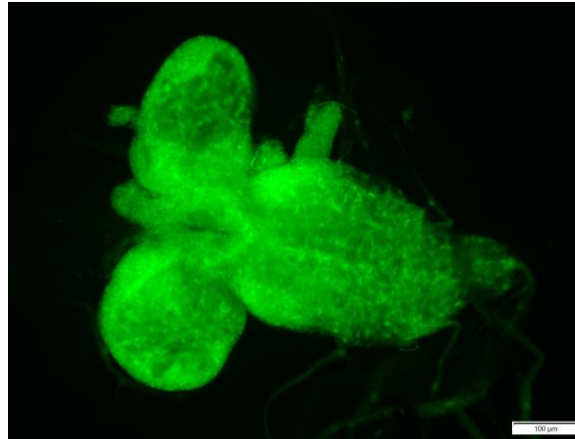
Results (cont.)

- P1G10

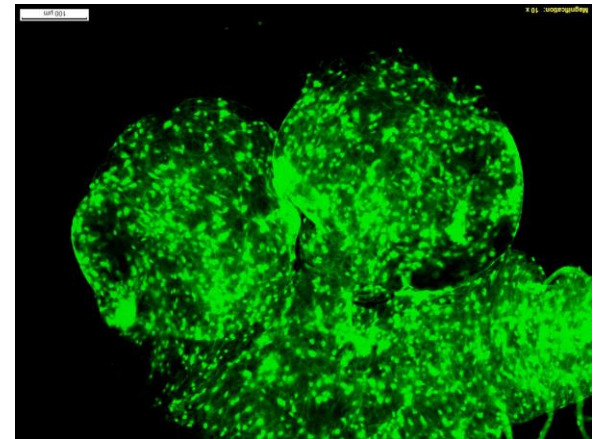
Glioma



Previous: (10 μ M)



Our screen: 300 μ M



	Initial # of Larvae	Total # of Larvae
Cross	21	6
Repo	21	8
Pteni	25	0



Future Directions

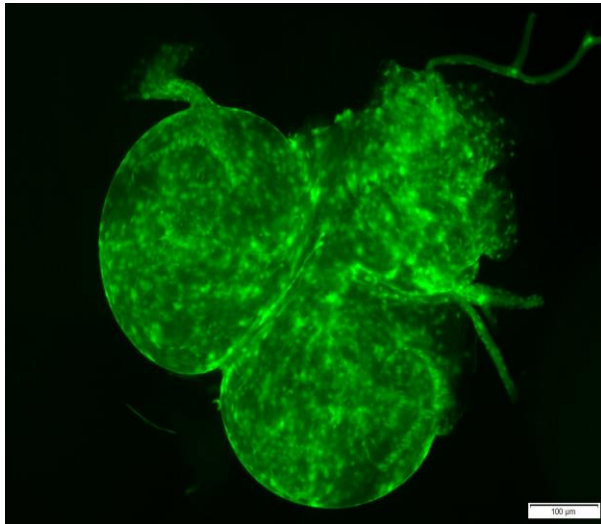
- EC50 Curve
 - Determines at what point the drug kills 50% of the population
 - Why is this important?
- Perform western blots
 - Determine proteins effected by the drugs, how pathways are affected
- Mammalian cell trials with Dr. Pitychoutis



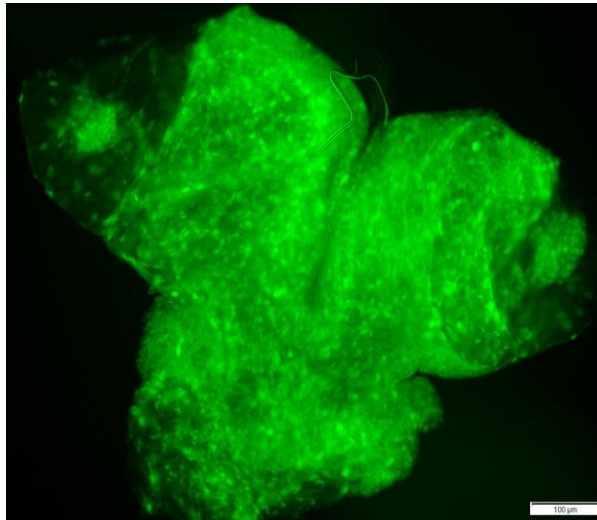
Future Directions (cont.)

- Additional preliminary screenings
- AZD 3759 (ongoing)

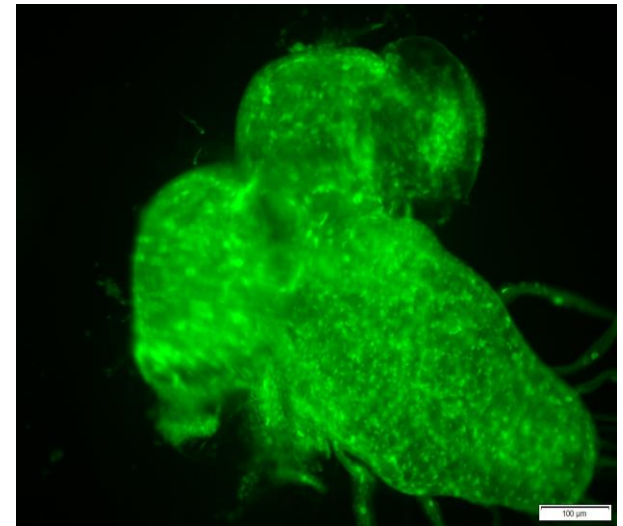
Repo control brain



Glioma brain



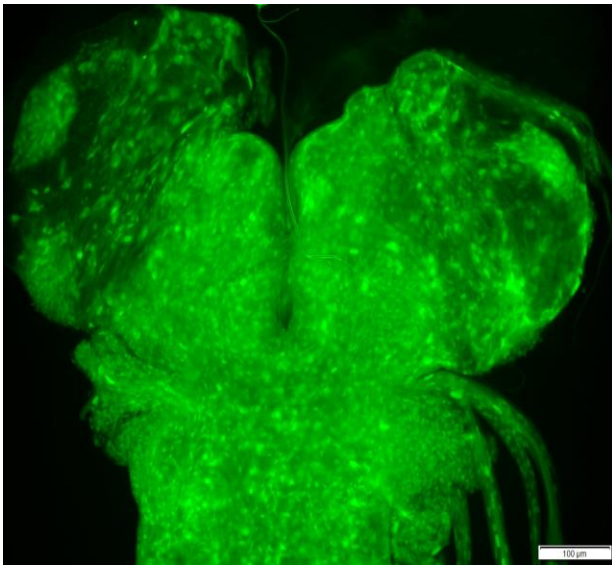
Glioma brain + Lapatinib (GW-572016) Ditosylate



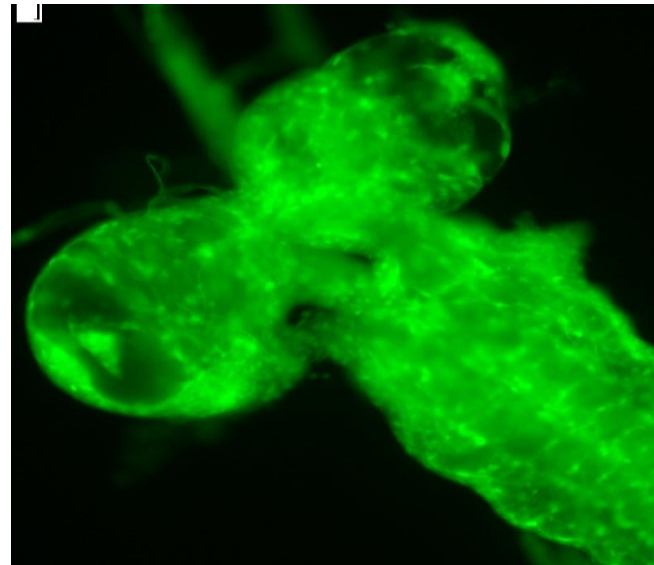
Future Directions (cont.)

- Gefitinib
 - In clinical phase 4, showing promise

Glioma

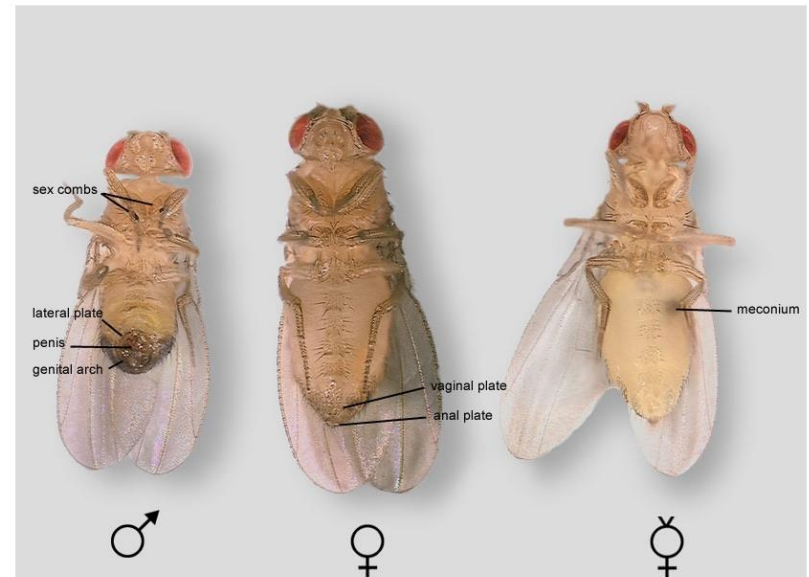


Glioma + Gefitinib (10uM)



Roadblocks

- Reestablishing fly colonies
 - Male : Female Ratios
 - Live organisms
- Virgin collection



Conclusion

- PIG8 & P1G10 at 300 μM
 - May be too toxic for larvae
 - Next step will be EC50 curve
- Utilize data to better understand how these tyrosine kinase inhibitors affect tumor growth/volume
 - Will help improve therapies and thereby prognosis of glioma patients



Acknowledgements



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Department



University of Dayton

References

- Katie Parker
 - Pi3k92E; EGFR cancer model
- Logan Roebke
 - *Pten*^{RNAi}, *ras*^{v12} pathway

