Senolytic Targeting of Adamantinomatous Craniopharyngioma: Dose-Response Characterization

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Background

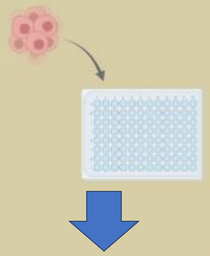
- **Adamantinomatous Craniopharyngioma (ACP)** is a rare, benign epithelial tumor that arises near the pituitary gland.
- The location of the tumor leads to significant morbidity including visual impairment, panhypopituitarism, obesity, and neurobehavioral deficits.
- ACP is a heterogenous tumor with abundant senescent like cells that contribute to pathology through the senescence associated secretory phenotype.
- Therapeutics that effectively target senescent cell populations could better treat ACP.

Methods

Senolytic Drugs and MOA:

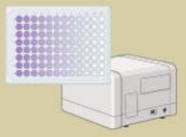
1. Dasatinib – BCR-ABL inhibitor and targets SRC family kinases
2. AZD5991 – Inhibitor of Mc1-1, a member of Bcl-2 family
3. Quercetin – Multiple possible mechanisms
4. Fisetin – Inhibits CDK6, suppresses NF-KB activation, downregulates anti-apoptotic genes

Plating of patient derived ACP 108 cells line onto 96 well plate

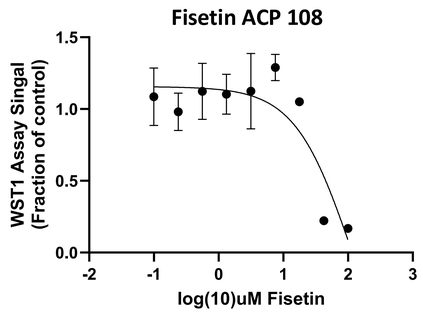


Dosing of Senolytic drugs

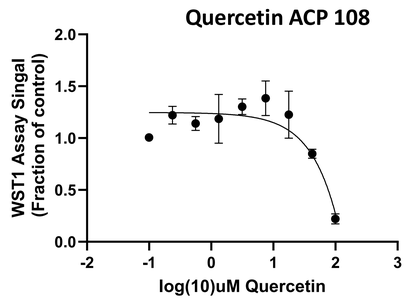
WST1/CCK8 cell assay for viability



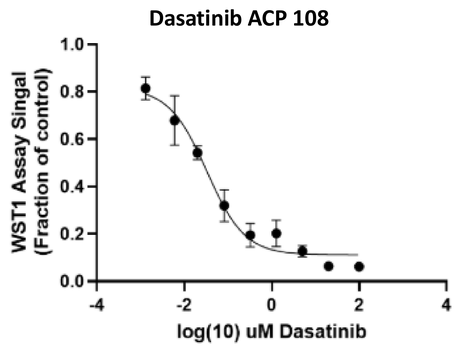
Results



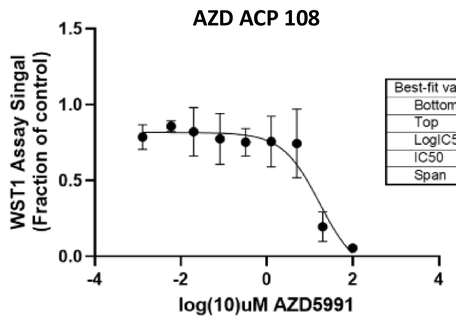
Bottom	-1.076
Top	1.156
LogIC50	2.036
IC50	108.5
Span	2.232



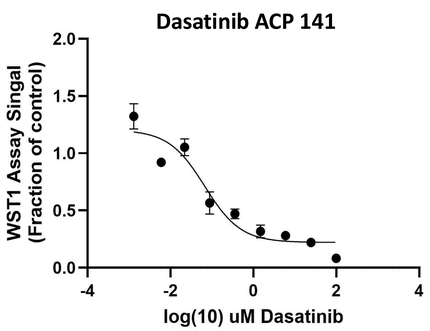
Bottom	-2404
Top	1.247
LogIC50	5.391
IC50	246317
Span	2405



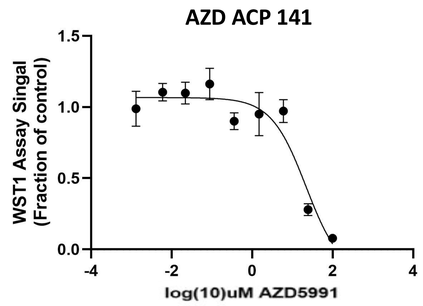
Bottom	0.1113
Top	0.8163
LogIC50	-1.484
IC50	0.03281
Span	0.7050



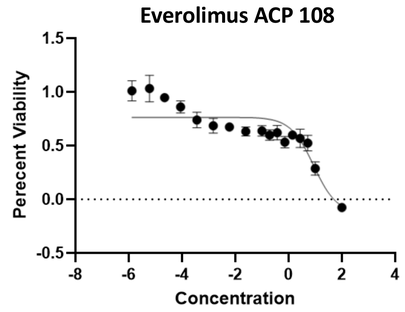
Best-fit values	
Bottom	-0.1155
Top	0.8166
LogIC50	1.229
IC50	16.95
Span	0.9320



Bottom	0.2214
Top	1.204
LogIC50	-1.176
IC50	0.06675
Span	0.9829



Bottom	-0.1867
Top	1.067
LogIC50	1.340
IC50	21.88
Span	1.253



Best-fit values	
Bottom	-0.1313
Top	0.7648
LogIC50	0.9334
IC50	8.578
Span	0.8962

Conclusions

- **ACP 108 cells show sensitivity to Dasatinib and AZD5991**
- **Quercetin and Fisetin have atypical IC50 curves**
- **Dasatinib has an IC50 around 0.029145 uM**
- **AZD5991 has a large IC50 range from 0.015 to 16.95 uM**

Strengths & Limitations

- **Experiments were done on two ACP cell lines**
- **Senescent aspect wasn't quantified or evaluated**
- **Only cell viability was measured**

Significance and Future directions

- **Expand experiments to different ACP cell lines**
- **Evaluate potential synergy between dasatinib and everolimus**
- **Evaluate senescent aspect after drug treatments**
- **Replicated experiments in 3D organoids to achieve better fidelity**

Funding Kids' Cancer Research