**Introduction**

Uveal Melanoma (UM) is a rare subtype of melanoma that grows from the melanocytes of the uveal tract of the eye. Although it’s more treatable if the primary tumor is isolated in the uvea, the poor prognosis of this disease is caused by its metastasis to the liver. The metastatic UM has only one FDA approved therapy and needs new therapeutic strategies urgently.

**Results**

**High Throughput Drug Screen to predict novel combination therapy strategies for UM**

Our initial high throughput combination drug screen with NT157 allowed us to predict a synergistic relationship between IGF-1R and HDAC inhibition in UM cell killing. A TargetMol Approved Drug library was used to test 2054 approved drugs for UM cell killing activity and eventually filtered down to 31 candidates for a combination screen. Belinostat was chosen for further investigation as it showed a good synergy score with NT157 combination (Figure 3).

**UM cell survival is efficiently blocked with combined treatment using Belinostat and NT157.**

Combination treatment with NT157 and Belinostat substantially improved the inhibition of UM cell survival over individual single agent treatments of UM cells as seen from MTT assays (Figure 4).

**Apoptosis was induced in UM cells treated with NT 157 and Belinostat in combination**

The routine western blots indicated that individual protein markers of the respective target pathways were reduced on treatments with IGF-1R pathway inhibitor (IRS-1) and HDAC inhibitor (HDAC 3, Acetyl Histone H3) (Figure 6). Combination treatment also strongly induced apoptosis in the UM cells as evidenced from the increase in cleaved PARP levels (Figure 6).

**Discussion**

UM being an extremely rare form of melanoma and very different from cutaneous melanoma lacks established therapeutic measures. Our preliminary data shows IGF-1R inhibition to be successful in partial reduction of UM cell survival. Single agent therapies usually do not work in melanoma in the long run, which prompted our high throughput combination drug screen with IGF-1R pathway inhibiting agent NT157. From the drug screen, we found that inhibiting the HDAC pathway in combination with IGF-1R pathway can lead to synergy in UM cell killing.

To validate these findings I tested the above combination treatment on UM cell survival. I observed that UM cells respond better to the combination treatment as compared to the single agent treatments. I also tried to determine the mechanism of improved UM cell killing from the combined treatment with apoptosis assays. Western blots for cleaved PARP indicated apoptosis induction in UM cells as a result of the combination treatments. The extent of response to the combination treatment is not the same in all cell lines and therefore in the future we plan to investigate the reason behind such differential responses. This would inevitably help improve the prognosis of this rare subtype of melanoma.

**Conclusion**

- IGF-1R pathway inhibition partially blocked UM cell survival
- Unbiased high throughput drug screen indicated synergy between IGF-1R and HDAC inhibition in UM cell killing activity.
- This was validated in in vitro UM cells based assays in the current study with nanomolar doses of each inhibitor
- Dual targeting of IGF-1R and the HDAC pathways improved UM cell killing over single agent treatments.
- Apoptosis was observed in low levels in the single agent-treated cells but even more for the combination treatments.

**References**