MASTER'S DISSERTATION TITLE

Biological Characterization of Myeloid-Epithelial-Reproductive Tyrosine Kinase (MERTK) Proteolysis Targeting Chimeras (PROTACs)

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SUMMARY

The advent of TPD has advanced the field of drug discovery, making it possible to degrade heretofore undruggable targets. PROTACs have extensively been applied to various targets including receptor tyrosine kinases. MERTK, a receptor tyrosine kinase has gained attention due to its central role in various pathologies and resistance mechanisms.

We sought to degrade this target with PROTACs hence this study aimed to characterize and understand their behavior at the molecular level. To achieve this, we combined *in-vitro* and *in-cellulo* assays. We developed proximity-based reporter assays based on the BRET system to monitor key events induced by these PROTACs in the cell.

We observed good penetration through the cell membrane and potent binding of compounds to MERTK, both *in-vitro* and inside cells. The PROTACs equally displayed strong binding to CRBN. Further, the PROTACs induced stable ternary complexes between MERTK and CRBN which had a strong positive correlation with the observed binding to MERTK. Ultimately, the PROTACs degraded MERTK in a concentration-dependent manner.

These detailed findings will provide insight for further optimizations and the development of degraders for MERTK. The established set of assays will allow a consistent, reproducible and efficient approach to the characterization of degraders.