**Lysine Demethylase 4B (KDM4B): A Novel Epigenetic Target in Atypical Teratoid/Rhabdoid Tumor (ATRT).**

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Atypical teratoid/rhabdoid tumor (ATRT) is a highly aggressive childhood brain tumor; current treatment options are limited with intensive chemotherapy and radiation which often create therapy-related toxicity; this is especially critical in this young patient population. Previous studies reported the loss of SMARCBI, a member of ATP-dependent SWI/SNF chromatin remodeling complex, is the hallmark molecular feature of ATRT, creating an overall epigenetic dysregulation of ATRT genome. This marks a potential avenue in the search for targeted therapy.

Epigenetic remodeling and transcription

Study Questions

1) Examine KDM4B’s (or KDM family genes) biological relevance in driving/maintaining the growth of ATRT cells
2) Determine mechanisms behind KDM4B function:  
   - how does KDM4B loss alter histone markers, chromatin remodeling and transcription
3) Can we use KDM4B as a potential therapeutic target?

Background: Atypical Teratoid/Rhabdoid Tumor (ATRT)

- Malignant central nervous system tumor in children
- 5-year survival of 35%
- Current therapy regimen: surgery, intensive chemo, radiation
- Salient molecular characterization: loss of SMARCBI gene
- Loss of function SWI/SNF chromatin complex and epigenetic dysregulation
- Different subgroups: TYR, SHH, MYC with various methylation patterns

What we learned so far

1) Examine KDM4B’s (or KDM family genes) biological relevance in driving/maintaining the growth of ATRT cells
   - KDM4B loss engenders decrease in ATRT tumor cell viability
   - KDM4B is differentially expressed at baseline in tumor cells and patient tumor samples vs control
   - Potential therapeutic window

2) Determine mechanisms behind KDM4B function:
   - KDM4B loss leads to global upregulation of H3K9Me3 expression
   - More heterochromatin/global suppression of genome

3) Can we use KDM4B as a potential therapeutic target?
   - Pharmacologic inhibition of KDM4B using small molecule tool compound differentially suppressed tumor cells without toxicity to normal human astrocytes and fibroblasts
   - IC50 not ideal, need better chemical inhibitor

Next steps/Future Directions

- Integrated H3K9Me3 Chromatin immunoprecipitation (ChIP) sequencing and RNA sequencing shKDM4B knockdown vs control cells analysis
- Identify pathways mediated by KDM4B
- KDM4B ChIP sequencing to explore its occupancy at promoters, enhancers and super enhancers in ATRT genome
- Enhance our understanding in its role in ATRT genome
- Elucidate role of KDM4B on chromatin remodeling
- Obtain novel KDM4B inhibitor and optimize for translational potential
- Test potential combination therapies
- Animal studies/preclinical testing

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