Conditional deletion of Mcl-1 in GFAP+ cells leads to a Vanishing White Matter disease-like phenotype

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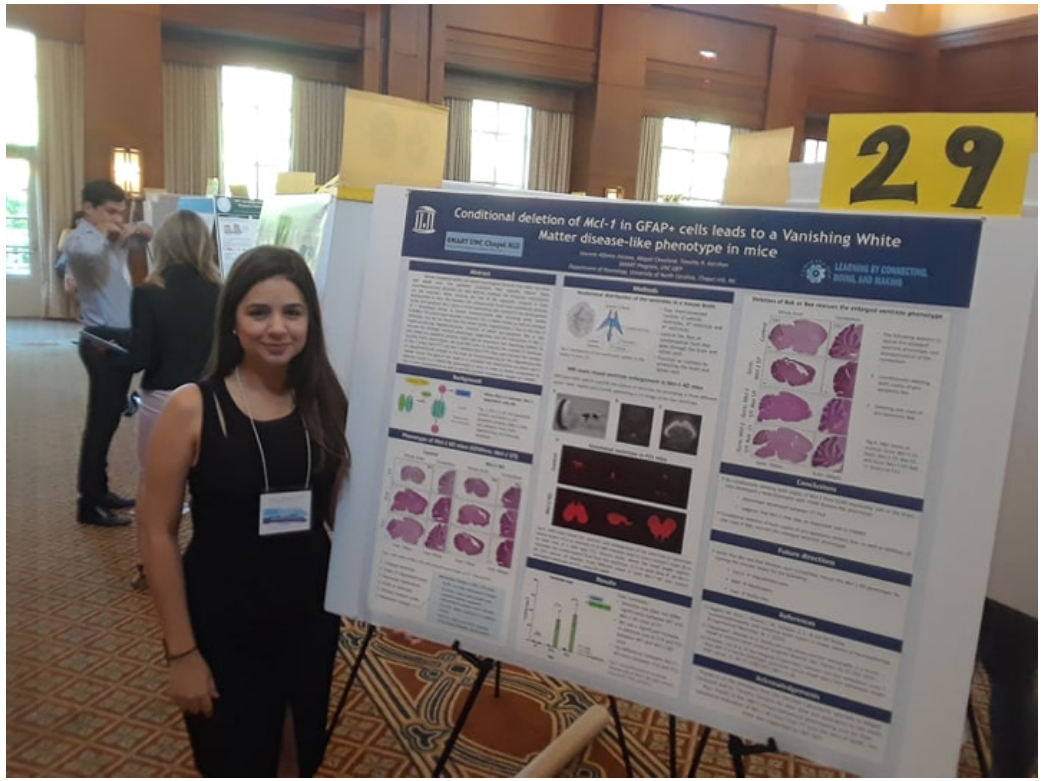

Research question:
What are the mechanisms by which *Mcl-1* deletion results in a Vanishing White Matter disease-like phenotype in mice? What is the change of ventricle size in mice with and *Mcl-1* expressed and deleted?

Why does it matter?
Human leukodystrophies are severe neurological diseases that affect the brain and spinal cord. Conditional deletion of the anti-apoptotic *Mcl-1* gene in GFAP-expressing cells resulted in the development of a phenotype similar to human leukodystrophy with vanishing white matter (VWMD). This phenotype included a dramatic loss of white matter as well as enlarged ventricles. Our lab has found that this white matter degeneration is due to the loss of myelin-producing oligodendrocytes. Deletion of either pro-apoptotic *Bax* or *Bak* rescued the enlarged ventricle phenotype, suggesting that the interaction of MCL-1 with these pro-apoptotic proteins might play an important role regarding VWMD. By elucidating the mechanisms by which *Mcl-1* deletion results in a VWMD-like phenotype in mice we would be able to identify possible therapeutic targets for VWMD.

- By conditionally deleting both copies of MCL-1 from GFAP-expressing cells in the brain, mice developed a leukodystrophy with VWM disease-like phenotype

- Significant increase in ventricle size between P7 and p21:
- Ventricle size increase not significant between wt and *Mcl-1* KO at P7
- Significant difference at P14 and P21 between wt and *Mcl-1* KO
- No difference of *Mcl-1* KO mice between P14 and P21

- Conditional deletion of both copies of pro-apoptotic protein Bax, as well as deletion of one copy of Bak, rescued the enlarged ventricle phenotype.

- All this data suggests that Mcl-1 may play an important role in the development of VWMD.

- All major changes in phenotype and behavior happened between P7-P14.

- The developmental study of the Mcl-1 protein as well as its relationship with pro-apoptotic proteins Bax and Bak, are relevant for future studies on Vanishing White Matter disease.