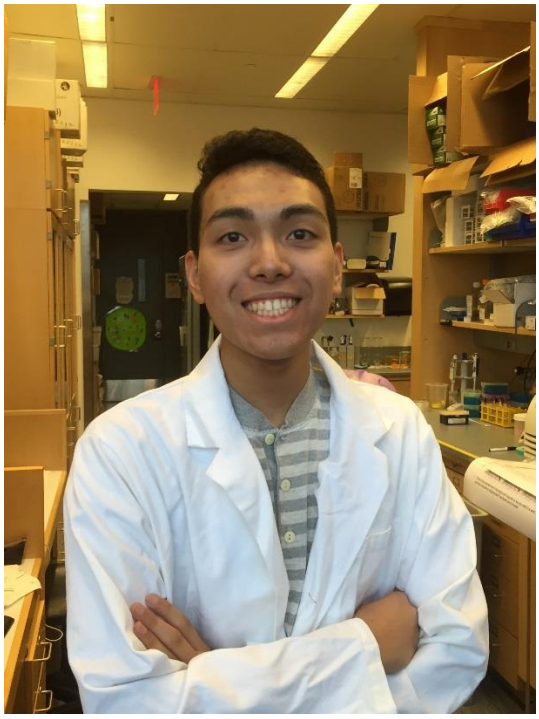

YY1 and CTCF Orchestrate/Coordinate a Looping Switch during Early Neural Development

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A long-standing question in biology is how our genome, 2 meters in length when stretched end-to-end, can fit inside the nucleus of a 10 micrometer cell? The answer lies in 3-dimensional folding patterns of the genome, which changes throughout development. Researching in the 3D genome and neurobiology lab of Dr. Jennifer Phillips-Cremins, we sought to understand the nuanced mechanisms of 3D genome folding during brain development.

CTCF is an architectural protein with a critical role in connecting higher-order chromatin folding in pluripotent stem cells. To elucidate the role for CTCF in the establishment of 3D chromatin configurations specific to the neural lineage, we analyze CTCF occupancy and fine-scale chromatin folding across cellular models of early development. Unexpectedly, we observe a sharp decrease in CTCF occupancy and expression during the transition from embryonic to adult brain tissues and a similar decrease from naïve/primed pluripotency to multipotent primary neural progenitor cells (pNPCs). Two classes of long-range chromatin interactions, (i) constitutive across cellular states and (ii) present in naïve/primed pluripotency but lost in pNPCs, are highly enriched for CTCF binding. CTCF occupancy mirrors interaction strength changes in constitutive and pluripotency-specific interaction classes. By contrast, pNPC-specific looping interactions do not exhibit enrichment for CTCF, suggesting that additional architectural proteins might mediate somatic cell type-specific connections. We identify the zinc-finger protein YY1 at the base of

pNPC-specific interactions between developmentally regulated genes and enhancers. pNPC-specific enhancers bound by YY1 participate in looping interactions, whereas enhancers without notable YY1 signal show a markedly lower propensity for 3D contacts. Importantly, YY1-mediated developmentally regulated interactions are often established de novo in pNPCs in a nested hierarchy within constitutive interactions anchored by constitutive CTCF. Together, our results support a model in which YY1 acts as a somatic architectural protein to connect developmentally regulated looping interactions; the location of YY1-mediated interactions may be demarcated/pre-marked in development by topological boundaries created by constitutive CTCF-mediated interactions.

Now in my 3rd year in the Cremins Lab, my research experience encompasses a full range of biological data science, from experiments to hypothesis testing to manuscript preparation. I am grateful for the breadth of knowledge that I have gained, from analyzing epigenomics data, running computational programs, interpreting results, culturing neural cells and helping to write and revise our manuscript. From May to August, I have been working alongside graduate student and mentor Jon Beagan, undergraduate student Caroline Lachanski and our PI, Dr. Jennifer Phillips-Cremins. Last summer, I assisted in culturing and harvesting embryonic stem cells that were used to create high-resolution 3D chromatin folding heatmaps. This summer, I really enjoyed my time learning our data-processing pipeline written in Python and additional bioinformatics programs MEME and Galaxy. I cultured mouse neural progenitors cells, which form elegant rosettes. Finally, I had the wonderful privilege of taking part in helping to create figures and writing, revising and reading the manuscript.

Thank you to CURF for empowering students interested in research. And a huge thank you to the Cremins Lab for your mentorship and support through the years.