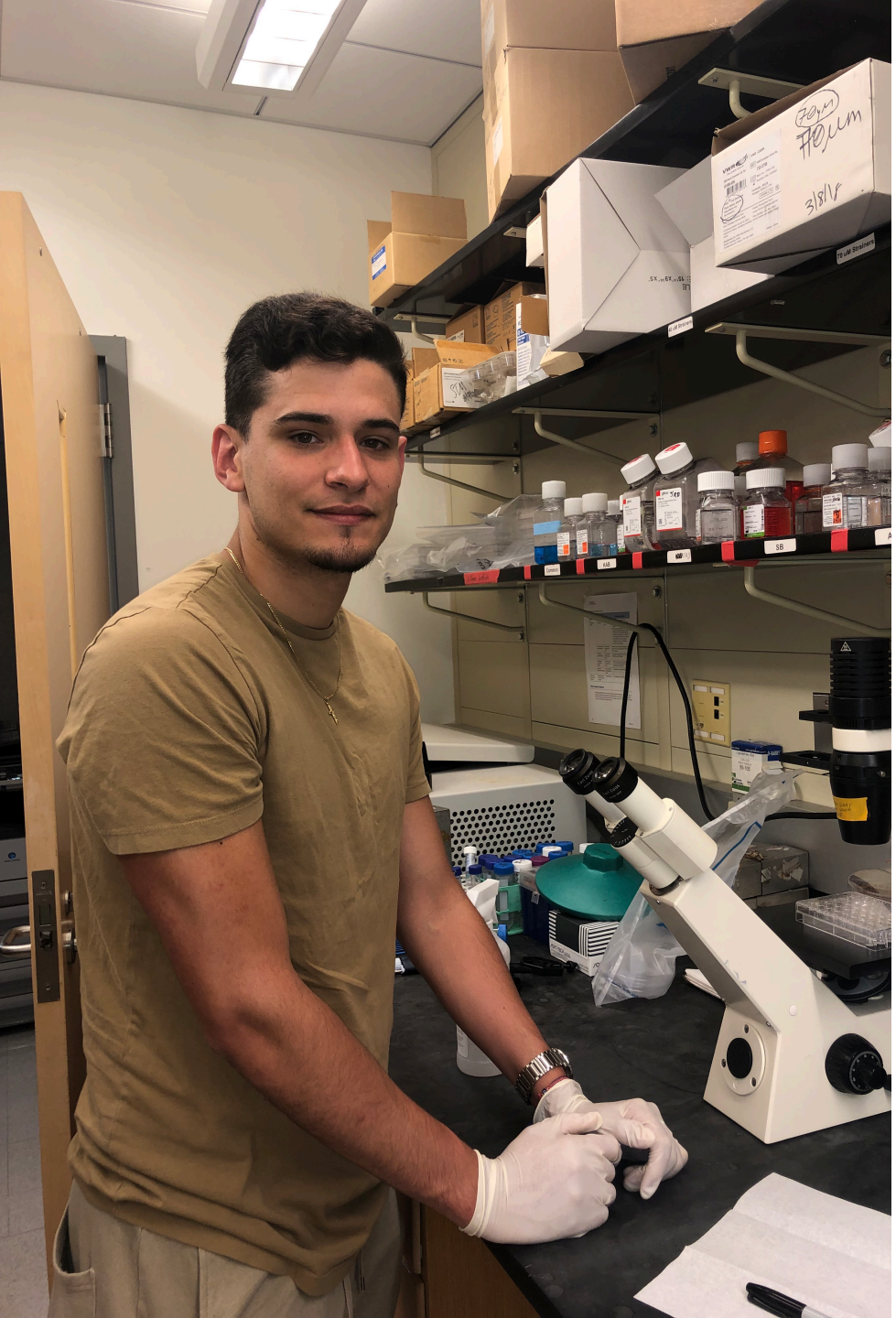

DETERMINING THE ROLE OF SOX9 IN THE BILE ACID-HIPPO SIGNALING PATHWAY IN THE LIVER

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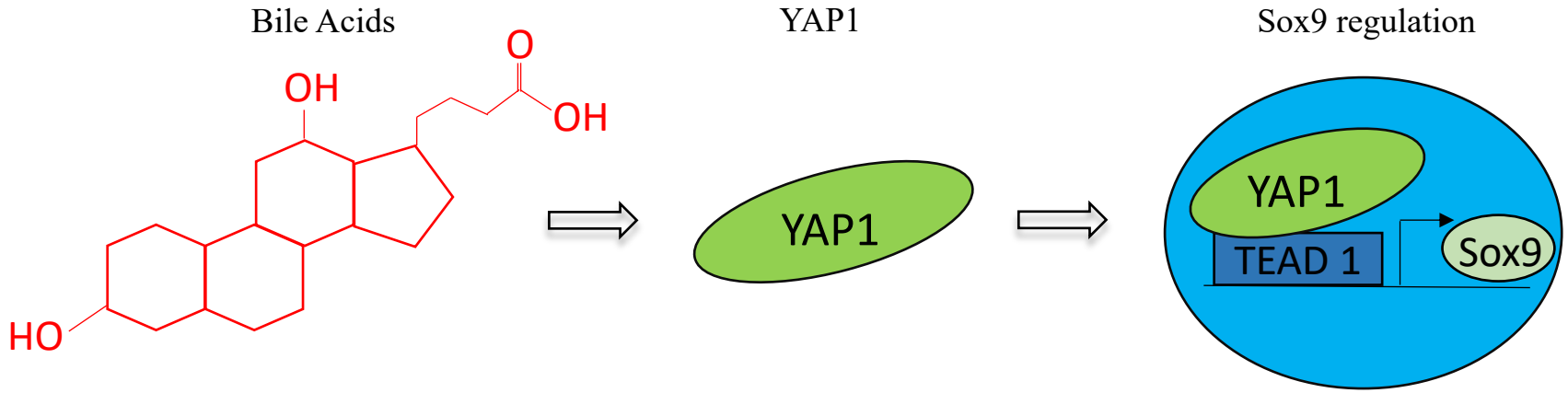
Do bile-acids (BAs) regulate the levels of Sox9 in the liver via the Hippo signaling pathway?



The liver is a vital organ, known to be capable of regenerating after substantial injury. Both main epithelial cell types, hepatocytes and biliary epithelial cells (BECs), play a crucial role in its regeneration.

Studies have shown induction of YAP1 signaling in BECs upon exposure to BAs, which are steroids produced from cholesterol.

YAP1 signaling is required for BECs survival upon BA exposure and essential for cell reprogramming upon liver injury.

In the intestine, Sox9 is known to be a stem/progenitor cell marker; however, its function and the means by which it is regulated is unknown in the liver.

Understanding the means by which BAs exposure in BECs regulates Sox9 via the Hippo-signaling pathway can give insight into how BEC reprogramming takes place upon liver damage, having important implications for advancing the treatment of liver diseases.

Results

To study this mechanism, I cultured organoids, a three-dimensional multicellular tissue construct that mimics its corresponding in-vivo organ. I treated these BEC organoids with: (1) primary BAs: cholic acid and chenodeoxycholic acid and (2) Verteporfin, a YAP1 inhibitor. We then examined gene expression levels after treatment.

My preliminary results show that treatment with CDCA causes a significant upregulation of direct targets of YAP1 in BEC organoids. Moreover, my results show that treatment with the YAP1 inhibitor causes significant downregulation in Sox9 expression.

Overall, these results allowed us to determine concentrations of BAs and Verteporfin that induced a significant response in Sox9 expression.

These results are essential for the general public because the understanding of such signal dynamics and heterogeneity in the liver in homeostasis and regeneration has important implications for advancing the treatment of liver diseases.