Elife digest.

1) How would you introduce the background to your research to someone who is completely unfamiliar with your field?
Neurogenesis is the process underlying brain development and it is executed by the neural stem cells, which generate neurons and glial cells. The proper regulation of neurogenesis requires that neural stem cells divide to amplify the population of cells in the growing brain. However, it also requires that these cells differentiate into mature neurons upon proper stimuli. The balance between these two activities is essential to achieve the right number of neurons without depleting the neural stem cells population. Such balance is achieved through a fine regulation of cell metabolism and gene expression. One layer of such regulation involves flexible processing of precursor messenger RNAs to yield multiple proteins from each gene. Several RNA processing factors modulate these mechanisms in the developing brain. One of them, SAM68, is highly expressed in neural stem cells and it was previously implicated in the pathogenesis of neurodegenerative diseases.

2) What exact question did you set out to answer?
SAM68 expression oscillates during mouse brain development, with a peak at times of intense neurogenesis and a sharp decline after birth. This observation suggested that SAM68 might be involved in the regulation of neurogenesis. Thus, we set out to investigate its role during brain development in mouse embryos.

3) What is the most important finding of your paper?
We found that the expression levels of SAM68 dictate the fate of neural stem cells. High expression promotes their self-renewal and amplification of the stem cell pool; low expression triggers their differentiation into neurons. We also linked SAM68 function to regulation of Aldehyde Dehydrogenase 1A3 (ALDH1A3) expression, an enzyme that fuels glycolytic metabolism in stem cells. We discovered that SAM68 binds an alternative polyadenylation signal in the ALDH1A3 transcript, preventing its premature termination and insuring expression of a functional enzyme. Thus, our study identifies SAM68 as a key regulator of neural stem cell self-renewal through maintenance of high glycolytic metabolism.

4) What is the most important next step and/or future challenge that follows on from your paper?
RNA metabolism plays a major role in brain development regulation and is often altered in neurodegenerative and intellectual diseases. Our future goal is to investigate whether functional defects in SAM68 are involved in such pathologies and to develop tools to rescue the molecular defects underlying them.