Gene expression is the process by which the genetic information contained in a piece of DNA, called a gene, is decoded to produce a gene product, often a protein. First, information contained in DNA must be copied by RNA polymerase II (RNAPII) into messenger RNA (mRNA) in a process called transcription. The mRNA transcripts are then edited to form a template for the proteins. One way to edit mRNA is through a process called alternative splicing, in which different fragments of the transcript are cut and pasted to make different versions of the final mRNA. This allows different instructions to be obtained from one gene. Transcription consists of three stages: initiation, elongation and termination. This process is tightly regulated, whilst mutations in the factors involved in RNAPII transcription underlie a variety of human diseases. The transcription rate is variable for different genes and for different parts of the same gene. The variable RNAPII speed has an impact on the amount and alternative splicing of mRNA, hence transcription kinetics determines the amount and type of proteins being produced.

Previously, I found that introducing a slowly transcribing RNAPII (referred to as “slow” RNAPII) to mice is lethal. I also showed that embryonic cells with “slow” RNAPII do not differentiate properly into neural cells. At the molecular level, I found that slow RNAPII is not efficient at transcribing long genes, which code for proteins important for neurons. The aim of this proposal is to understand how transcription rates are regulated in neurodevelopment and what the consequences of perturbed transcription elongation are for brain development and genome stability. The project consists of three specific goals: 1) to find mechanism of RNAPII elongation rate regulation in neurodevelopment, i.e. define the role of chromatin and proteins interacting with RNAPII, 2) to establish if perturbed RNAPII elongation has a role in Autism Spectrum Disorder (ASD) aetiology, 3) to uncover how controlled transcription rates function in preserving genome stability. The proposed project will expand our understanding of transcription mechanisms in physiological and pathological processes. We will publish the results in the international scientific journals. Overall, scientific advances from this study, that is better understanding of the mechanisms of gene regulation and molecular underpinnings of the disease, will contribute to better disease diagnosis and drug development.