

## **Project 9.1. Cytoplasmic polyadenylation as a central regulator of physiological processes**

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### **Background:**

Poly(A) tails generated by canonical poly(A) polymerases during mRNA 3' formation are essential for mRNA stability and translation.

It is now appreciated that poly(A) tail dynamics is more complex than previously suspected; deadenylated mRNAs in the cytoplasm can be degraded, uridylated or stored in a dormant state to be later re adenylated to activate protein synthesis. Cytoplasmic polyadenylation was mostly studied in the context of gametogenesis and in synapses, where the transcriptional activity is limited. Surprisingly, mouse lines devoid of the well known cytoplasmic poly(A) polymerase GLD2 display no apparent phenotypes. We recently described a novel family of cytoplasmic poly(A) polymerases, TENT5 (FAM46), comprising four members in vertebrates (Mroczek et al. & Bilska et al. Nat Comm 2017,2020). TENT5C acts as a tumor suppressor in multiple myeloma, while mutations in TENT5A lead to a rare disease osteogenesis imperfecta. We have generated KO mouse models for all TENT5 genes and detected a variety of different phenotypes affecting several organs and biological processes: gametogenesis, growth, skeletal development, hematopoiesis, immune response, and behavior. Moreover, analysis of the KO of worm TENT5 orthologue revealed dysfunction of innate immunity. Thus, TENT5 proteins contribute significantly to metazoan physiology and, more generally, that cytoplasmic polyadenylation plays a much broader role than previously anticipated, opening a new area of important research.

### **Aim:**

We aim to dissect functions and mechanisms of cytoplasmic polyadenylation by TENT5 in innate immunity, erythropoiesis, and neuronal physiology. Unique animal models constructed using CRISPR/Cas9, combined with advanced transcriptomic and proteomic approaches, will be used to achieve our goals.

Several positions are available in the lab. The exact PhD project will depend on the particular skills and preferences of the student

We are looking for students with experience in work with animal models (mouse, *C. elegans*), RNA biology, or bioinformatics.