2020-11-30

EuReCa International PhD Program

PhD thesis project

2021 Call for application

Identification and targeting of lncRNA sequence motifs regulating melanoma oncogenesis

General information

Call	2021
Reference	2021-10-SHKUMATAVA
Keyword(s)	Long noncoding RNAs; RNA regulatory motifs; Skin melanoma; Zebrafish, human cell lines; RNA therapeutics

Director(s) and team

Thesis director(s)	Alena Shkumatava
Research team	LincRNAs in vertebrate development
Research department	U934/UMR3215 – Genetics and Developmental Biology

Description of the PhD thesis project

We are investigating in vivo functions and mechanisms of action of long noncoding RNAs (lncRNAs) that have emerged as key regulators of diverse biological phenomena and are implicated in many human cancers including melanoma.

Metastatic skin melanoma is among the cancers with the highest mortality despite recent progress in targeted and immune-check point therapies. While lncRNAs represent an untapped source of therapeutic targets, their precise molecular functions during cancer initiation and progression remain elusive, often due to the lack of suitable molecular tools and in vivo models.

Using an inducible zebrafish skin cancer system that closely parallels the process of skin cancer development in humans, we discovered a lncRNA that altered melanomagenesis by accelerating melanoma initiation, increased tumor progression (i.e. tumors reached earlier a more advanced tumor stage) and spread of metastasis in vivo. Remarkably, the human lncRNA ortholog has been found to be misregulated in human metastatic melanoma compared to primary melanoma and its expression in the zebrafish lncRNA mutant inhibited accelerated melanoma progression, indicating that its molecular function is highly conserved throughout evolution.

Our project aims to investigate the molecular mechanism that underlies the conserved tumor suppressor function of this lncRNA during melanomagenesis with the overarching goal of defining functional lncRNA motifs that may serve as therapeutic target sites.

To achieve our goals, we use a combination of in vivo models and molecular tools including our novel incPRINT technology for identification of RNA-protein interactions and their targeting with small molecule inhibitors. We will test the functionality of the identified lncRNA motifs using relevant human melanoma cell lines and zebrafish.

Thus, our research program will provide critical molecular insights into the biology of lncRNA motifs, potentially uncovering novel drug target sites for melanoma patients.

International, interdisciplinary & intersectoral aspects of the project

The project is based on interdisciplinary approaches at the forefront of RNA biology, comparative genomics, cancer cell biology, advanced high throughput biochemical methods and first steps towards unbiased drug discovery.

The student will develop specific skills in all mentioned above disciplines. It includes collaborations with the international experts in comparative genomics (Weizmann Institute, Israel) and with the experts in normal and pathological development of melanocytes (IC). Discovery of drugs targeting RNA-protein interaction will be elaborated through collaborations with chemists.

The student will be exposed to the ongoing spin-off creation specializing on drugs targeting RNA-protein interactions and will interact with a Versailles-based company on advanced CRISPR-Cas9 tools.

Recent publications

1) Pérez Rico YA, Barillot E, **Shkumatava A.** Demarcation of topologically associating domains is uncoupled from enriched CTCF binding in developing zebrafish. iScience, 2020 May 22;23(5):101046. doi: 10.1016/j.isci.2020.101046

2) Graindorge A, Pinheiro I, Nawrocka A, Mallory AC, Tsvetkov P, Gil N, Carolis C, Buchholz F, Ulitsky I, Heard E, Taipale M, **Shkumatava A.** In-cell identification and measurement of RNA-protein interactions. Nature Communications. 2019 Nov 22;10(1):5317. doi: 10.1038/s41467-019-13235-w.

3) Lavalou P, Eckert E, Damy L, Constanty F, Majello S, Bitetti A, Graindorge A, **Shkumatava A.** Strategies for genetic inactivation of long noncoding RNAs in zebrafish. RNA, 2019 May 1. pii: rna.069484.118. doi: 10.1261/rna.069484.118.

4) Bitetti A, Mallory AC, Carrieri C, Golini E, Carreño Gutierrez H, Perlas E, Pérez-Rico YA, Tocchini-Valentini GP, Enright AJ, Norton WHJ, Mandillo S, O'Carroll D, **Shkumatava A.** MicroRNA degradation by a conserved target RNA regulates animal behavior. Nat Struct Mol Biol. 2018 Feb; doi: 10.1038/s41594-018-0032-x.

5) Pérez Rico YA, Boeva V, Mallory AC, Bitetti A, Majello S, Barillot E, **Shkumatava A.** Comparative analyses of super-enhancers reveal conserved elements in vertebrate genomes. Genome Res. 2017 Feb;27(2):259-268. doi: 10.1101/gr.203679.115.

Expected profile of the candidate

Highly motivated students interested in biology of regulatory noncoding RNAs in an in vivo context are encouraged to apply.

Applicants should have a strong desire to explore cell biological phenomena in an in vivo context, and should show solid capacity for independent and creative thinking in a collaborative environment.
Background in RNA biology, cell biology and/or cancer biology is strongly recommended. Background in bioinformatics is a plus but not compulsory.

The successful candidate is an enthusiastic individual, keen to work both on collaborative and independent projects.