INSTITUTE OF BIOCHEMISTRY AND BIOPHYSICS
POLISH ACADEMY OF SCIENCES

1. **Research Unit:** Laboratory of Transcription Mechanisms
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5. **Project title (English):** Molecular mechanisms linking RNA polymerase III mutations to Hypomyelinating leukodystrophy.
6. **Project title (Polish):** Mechanizm molekularny łączący mutacje polimerazy III RNA z rozwojem leukodystrofii typu HLD
7. **Description of the project (up to 500 words):**

DNA stores genetic information, that is expressed to produce functional copy of DNA - RNA. Gene expression is carried over by specialized multi-protein complexes RNA polymerases. Some RNAs encode proteins and undergo translation. However, protein coding genes comprise only 2% of the human genome. They are scattered unevenly across chromosomes and are surrounded by non-protein coding genes, that are much more abundant. The most abundant non protein coding RNAs are ribosomal RNA (rRNA) and transfer RNAs (tRNAs), which are elements of essential machinery producing proteins in the cell. Loss of function in fundamental machinery such as RNA polymerases or translation machinery is lethal, so only minor defects are tolerated, generating disease states.

This project will investigate the molecular mechanisms of mutations in RNA polymerase III (RNAPIII), producing tRNAs. RNAPIII mutations underlie a group of rare inherited diseases called RNAPIII-related leukodystrophy associated with loss of myelination, or Hypomyelinating leukodystrophy (HLD). HLD is a disorder that affects the nervous system and involves abnormalities in white matter in brain. White matter consists of nerve cells (neurons) covered by a fatty (lipid) substance called myelin, which is essential for proper brain functioning. It surrounds neural fibres, provides electrical insulation and is responsible for fast and efficient conduction of nerve impulses.

This project aims to provide answer to how mutations in fundamental machinery of RNA polymerase III, essential for every cell, lead to the tissue-specific disease. We aim to identify major cellular pathways affected by HLD-related mutation. To do this we will genetically modify human cell line to introduce RNAPIII HLD mutations. We will investigate abnormalities in RNA production and protein production in relation to the healthy cells. In our interdisciplinary approach, we will generate a number of biological data using high throughput sequencing technology and analyse them using state-of-the-art data science methods.

Our results will help understand structure of human genome, the relation between protein coding and specific non-protein coding genes – tRNAs. We should be able to identify genes and pathways that are directly affected in RNAPIII HLD and can be potentially treated. If successful, we would like to continue our research utilizing brain mimicking structures called organoids and study myelination process in the laboratory.

8. **References related to conducted /planned research (maximum 3)**:
    - https://doi.org/10.1074/jbc.ra118.006271
    - https://doi.org/10.1101/gr.205492.116
    - https://doi.org/10.1038/s41594-020-00555-5

9. **Scholarship amount (net):** please contact the project auxiliary supervisor: Dr Tomasz W. Turowski (tomasz.turowski@ibb.waw.pl)