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The interview with the author of the PhD thesis: „Molecular basis of deoxyhypusination”

Could you briefly introduce your field of research to our readers?

I can answer this question from two different perspectives. From a technical point of view, I work in the field of structural biology – a discipline that literally allows us to „see” proteins: their structure, how they function, and how they interact with other molecules. In my work, I primarily use macromolecular crystallography and cryo-electron microscopy, which enable us to capture proteins in action. I complement these methods with techniques from molecular biology, biochemistry, and biophysics in order to understand the studied processes as thoroughly as possible.

From a biological point of view, my main area of interest is hypusination – an extremely rare and unique post-translational modification of a lysine residue, which occurs exclusively in a single protein: the translation factor eIF5A. This modification is essential for the proper functioning of cells – both healthy and cancerous. It proceeds in two steps and is catalyzed by two enzymes: deoxyhypusine synthase (DHS) and deoxyhypusine hydroxylase (DOHH). As part of my doctoral project, I focused mainly on the first step – the reaction catalyzed by the DHS protein.

How can your research contribute to the development of new drugs?

The hypusination process plays a crucial role in maintaining cellular homeostasis. Its excessive activity is observed in cancer cells, while its deficiency is associated with neurodevelopmental disorders. A better understanding of the mechanism behind this modification, especially at the structural level, enables the design of selective inhibitors or modulators of the enzymes responsible for the process. My research therefore paves the way for the development of targeted therapies that could be used in the treatment of cancer or rare diseases.

What has been the biggest challenge in your work?

The biggest challenge was developing and optimizing the preparation of samples for both crystallographic experiments and those using cryo-electron microscopy. Working with proteins is often unpredictable – their production, purification, crystallization, or imaging requires a great deal of precision, patience, and consistency. However, I must admit that these difficult moments have been the most valuable – they taught me the most, and the experience I gained continues to benefit me in future projects.

How did the resources provided by Cyfronet support your research?

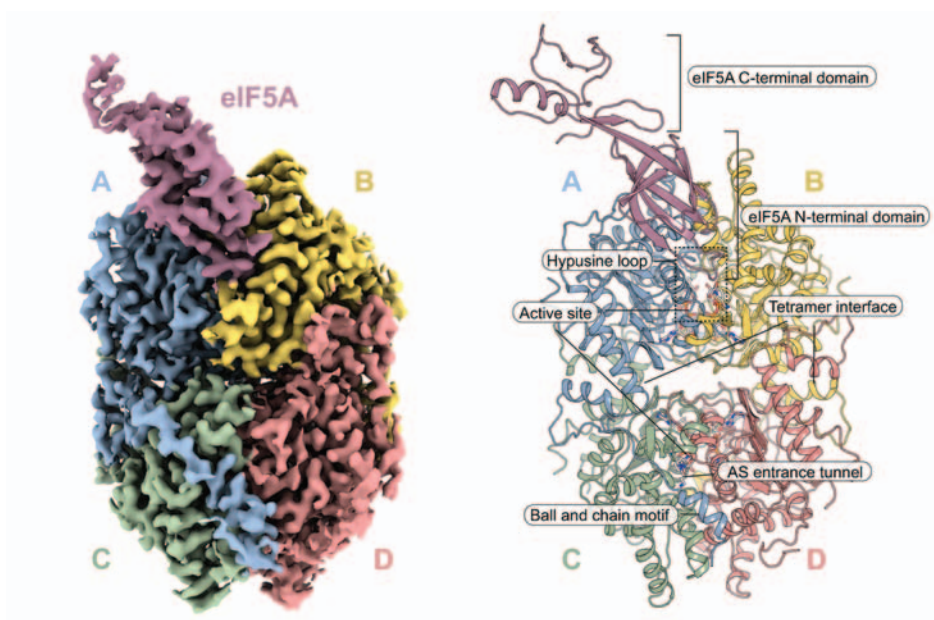
The computational resources offered by Cyfronet played a crucial role, especially during the analysis of structural data. In cryo-electron microscopy, we generate vast amounts of data, and processing

them requires access to high-performance computing systems. Thanks to Cyfronet's infrastructure, I was able to efficiently analyze cryo-EM data, which significantly accelerated the progress of my research.

I directly used these resources while working on the structure of the parasitic DHS-eIF5A protein complex, which was published in *The FEBS Journal* in 2024. This publication is one of three papers that make up my doctoral dissertation. However, it's worth emphasizing that only a small portion of the structures we obtained have been published, so the results presented in the papers reflect just part of the use of the infrastructure. It's also important to highlight the "behind the scenes" aspect of the publication process – namely, the multi-step optimization of samples. The Ares and Athena supercomputers were my everyday tools, used, among other things, to validate successive iterations of optimized cryoEM samples.

What advice would you give to those just beginning their scientific careers?

Scientific work is about constantly pushing your own limits – it often means stepping out of your comfort zone, for example through international stays or participation in new projects. My motto is: *"Feel the fear and do it anyway."* It's worth exploring different paths, getting involved in diverse initiatives, and testing your ideas. I also encourage applying for all kinds of grant and scholarship programs – they're a great way to grow and build your research independence. Even if something doesn't work out the first time, every attempt teaches you something valuable.



Cryo-EM map and corresponding molecular model of human eIF5A-DHS complex solved by cryoEM.