PROPEL
Protein Rigid Organization for Powered Engineered Locomotion

ERC CONSOLIDATOR GRANT 2025 – QUESTIONS AND ANSWERS

What is the purpose/goal of the PROPEL project?
The goal of the project is to create the first completely *de novo* designed protein motor—that is, a protein that can walk along a track in a specific direction and carry cargo. Dr. Ljubetič and his team will design the proteins using advanced artificial intelligence tools, and their movement will be studied with sensitive single-molecule measurements. The motors will be powered by the principle of a diffusion ratchet (Brownian ratchet), which converts random motion into directed motion with the help of an energy source and asymmetry in the track**.**

At its core, the project is basic science; however, synthetic protein motors have enormous potential for future applications—from self-repairing smart materials to new treatments for neurodegenerative diseases.

What are protein motors and what do they do?
Protein motors, or protein walkers, are proteins that consume energy and can perform work. Natural protein motors are essential for life, as they copy DNA, remodel cellular membranes, and transport molecules to where they are needed in the cell. For example, the motor myosin, which walks along actin filaments, enables us to contract our muscles and move.

Why is it important to design synthetic proteins/protein motors?
Natural protein motors evolved to function inside cells, but they are not suited for many new applications envisioned by scientists (such as drug delivery or creating self-repairing materials). Natural motors are not stable outside cells, and they are harder to control or "program." In contrast, *de novo* designed proteins are highly stable—they can even be heated to 90 °C without losing function. They are also built modularly (from independent components), which makes them easier to modify and easier to program. This allows them to be adapted for tasks that natural protein motors cannot perform.

What prevents us, at present, from designing fully *de novo* protein motors from scratch?
Proteins are extremely difficult to design—the first completely de novo designed protein was created only in 2003. Proteins are made up of 20 amino acids, and each amino acid can adopt many different positions. Thus, a small protein with 100 amino acids has 1.2×10^{30} possible sequences and over 6.5×10^{177} possible shapes. These are dizzyingly large numbers. However, scientists have made major progress in this field.

The rapid development of protein design methods has been accelerated in recent years by advances in artificial intelligence. In 2024, the Nobel Prize in Chemistry was awarded for breakthroughs in protein structure prediction and design. For the first time, we now have tools that may allow us to design entirely new protein motors.

What exactly will you try to achieve in the process of building these protein motors?
We will try to build proteins that can move directionally along *de novo* designed protein tracks and at the same time transport cargo or carry out other useful tasks. This is necessary for all future applications.

What is the difference between *de novo* designed protein motors and the motors that can be found in our cells?
An appropriate analogy would be the comparison between the wings of an airplane and the wings of a bird. Designed proteins are more stable, we will understand them better and therefore program them more easily. Natural proteins are more »refined«, but also more sensitive.
There is also a difference in the energy source. Natural proteins use the molecule ATP, while designed proteins will use various other energy sources, such as electric fields.

How are the "nanorobots" developed in this project different from existing ones?
So far, nanorobots have mostly been made from DNA, but they move very slowly and cannot self-assemble inside living cells.
De novo designed protein nanorobots do not yet exist.

Why is this project important for the National Institute of Chemistry and for the entire Slovenian scientific community?
The project will enable faster development of protein design methods in Slovenia. Beyond its scientific value, it also demonstrates that Slovenian science is comparable to the best in Europe, as only the top scientists receive ERC grants. With strong support from the government and institutes, Slovenia can conduct world-class research. This basic science could, with a bit of luck, also benefit other fields, such as the development of new medicines or smart materials.
Dr. Ljubetič learned the latest protein design methods in the laboratory of a Nobel laureate, and upon returning to Slovenia, he brought this technology to the National Institute of Chemistry.

What applications could follow from this ERC project? Can you give one potential example?
ERC projects support basic science. Real applications will therefore only emerge after the project is completed.
However, the potential is enormous! Protein nanorobots might, in 30 years, treat neurodegenerative diseases by removing protein plaques from cells, assemble self-healing smart materials, or even power fully synthetic cells.
Similarly, just as the first computers 70 years ago had only 92 unreliable transistors, today each of us carries trillions of transistors in our pockets that allow us to connect to Facebook.

How long will the project last, and how much is it worth?
The project will last 5 years and is worth €2,000,000. So far, only six ERC Consolidator grants have been awarded in Slovenia, and this is also the first ERC CoG in the life sciences in the country.

What cutting-edge research equipment will be used in the project?
We will use a wide range of equipment, from a GPU-based computing cluster to specialized devices for sorting proteins by size. I would like to highlight two particular microscopes.

The first is a TIRF fluorescence microscope, which will allow us to track individual molecules. This will enable us to observe the movement of protein motors in real time. The system also includes optical tweezers, which will allow us to measure the forces generated by the motors.
The second is a Cryo-EM microscope, which will allow us to determine the precise structure of the motors and verify whether our protein designs match reality.

Why are you so fascinated by proteins—what makes them so special?
Proteins are truly amazing and versatile molecules. They are the molecules that mother nature has chosen to perform most of the functions essential for life. Proteins are enzymes that can accelerate complex chemical reactions, they are a key part of our immune system and protect us from viruses and bacteria, and in the form of collagen fibers they can also provide structural support. In short, proteins are really "cool," and my favorite are those that can move or change their shape.