prognos

HFSP CASESTUDY

Research Grant: Molecular Motors

A modular protein design route to exploring the operating principles of molecular motors

Authors
Dr. Thomas Stehnken
Michael Astor Jakobus Jaspersen
Isabel Schöfl Miguel Wahle
Dr. Jürgen Wastl (Kathryn Weber Boer
Helene Draux

Client
Human Frontier Science Program
Organization (HFSPO)

Date
October 2025

Project Title	**A modular protein design route to exploring the operating principles of molecular motors**
Starting Year	2007
Principal Investigator	Heiner Linke
Collaborators	Paul Curmi, Nancy Forde
Countries	USA/Sweden, Australia, Canada
Disciplines	Nanophysicist, Structural biologist, Biophysicist
Task	Understand and recreate the operating principles of molecular motors
Key output	Functioning artificial molecular motor, corresponding models and insights into the working of motor proteins

In addition to the cited documents, interviews with the researchers and HFSP data were used as sources. Furthermore, quantitative analyses were carried out using the Dimensions Database.

1 Overview

This case shows an international, interdisciplinary effort to understand and recreate the operating principles of molecular motors. The HFSP-funded project pursued a modular protein design route: assembling nonmotor protein parts into artificial machines to test, by construction, what is required to generate directed motion at the nanoscale. Two complementary strands structured the work: a 'Lawnmower' motor, which chews up the protein track as it moves, so it can only go forward, and a 'Tumbleweed' walker, which walks along a DNA track. Work was coordinated across three continents and disciplines, pairing theory and simulation with protein engineering and single-particle experiments. The goal was not simply to catalogue designs, but to develop and verify general design rules for converting chemical energy into mechanical work with proteins. It is an example of how HFSP funds projects that are ahead of their time and thereby pushes the frontiers of science. The project also illustrates that basic research often requires years or even decades to reach key milestones, not least because these frequently depend on advances in other fields.

2 The Project

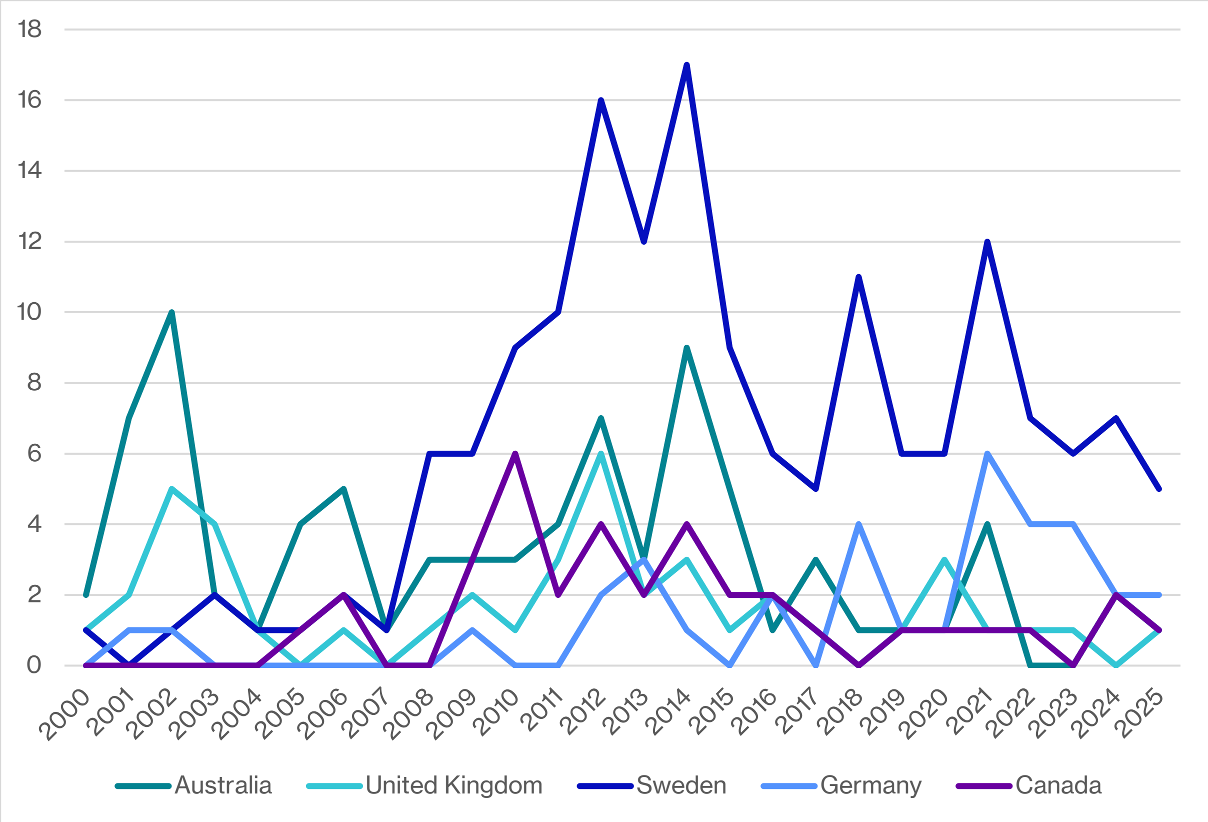
Motor proteins or molecular motors are big molecules that are essential for the functioning of every complex life form. They serve as transports and force generators within cells and are highly complex motors operating at the limit of what is physically possible. The starting point for the project was a simple proposition: if we truly understand the rules behind molecular motors, we should be able to build one from scratch. Conversely, the attempt to construct a molecular motor would yield substantial insights into the functioning of such motors. A truly interdisciplinary team from physics and biology came together with the explicit intent to test this by recreating a molecular motor. This was an extremely ambitious, high-risk project, and it could not have been initiated without HFSP funding both because of its high level of risk and because of the transcontinental nature of the international collaboration.

The project pursued two complementary architectures to probe operating principles. The burnt-bridge ‘Lawnmower’ concept uses a protein or nanoparticle hub densely decorated with protease ‘blades’ that cleave a substrate ‘lawn’ of peptides on a surface; each cleavage irreversibly removes a binding site and biases Brownian motion forward, converting chemical free energy into net displacement. In parallel, the ‘Tumbleweed’ walker uses modular ligand-gated DNA-binding domains arranged on a designed protein chassis to achieve cyclic, hand-over-hand stepping along a patterned DNA track. Across both strands, the scientific aim was to translate qualitative principles from biological motors into quantitative design rules: balancing reversible attachment and irreversible steps, coordinating multi-domain binding, and tuning binding energies and geometry for processivity.

The practical barriers to the project were substantial. The required tools did not exist, interfaces between modules were uncertain, and progress demanded extensive modelling to derive workable design constraints. Within the duration of the HFSP project, the goal of constructing a molecular motor could not be achieved. Nevertheless, significant progress was made in understanding the design challenge and in developing simulations and methodologies. This also included exploring various dead ends and determining what did not work.

A problem arose in that, once HFSP funding had ended, no other funders were available to continue the project in its original configuration. Remarkably, the researchers nevertheless succeeded in pursuing the project further, in different configurations and with different funding sources (e.g. from the European Research Council) while the lab infrastructure and tool-chain matured. A crucial factor in making this possible was that smaller, publishable advances could be achieved along the way. Still, it speaks to the high intrinsic motivation of the researchers. Nonetheless, HFSP was essential to provide the initial spark to get the project and collaboration going.

Figure 1: Top 5 countries for collaborative publications of the PI over time



Source: Dimensions Database.

One way to show the long-lasting collaborations between the team members is to look at their joint publications over time. The figure above confirms that the collaborations enabled by the HFSP project continued well beyond the project's funding period and resulted in numerous internationally collaborative publications.

Progress benefited from complementary laboratory strengths, a culture of embracing uncertainty, sustained cross-site meetings, and substantial modelling to extract design rules before full experimental control was possible. Another key factor in the project's success was the interdisciplinary team. Without specialists from different fields, it would not have been possible to carry out the project. Constraints included missing tools at the outset, the experimental difficulty of coupling modules without losing function, limited staff capacity, and the time required for ambitious integration. In retrospect, slightly sharper task partitioning at selected milestones might have reduced friction while preserving the gains from integration.

Ultimately, in 2025 – almost 20 years after the project began – the project reached its initial goals. The researchers succeeded in (re)constructing simple functional molecular motors and publishing the models and results. The team had produced a protein 'chassis' assembled from orthogonal coiled-coil building blocks for multi-domain mounting and a working 'Lawnmower' motor that achieved autonomous, track-consuming motion. Completing the initial set of goals, the Tumbleweed route advanced from blueprint to implementation, demonstrating autonomous stepping on a DNA track using modular protein parts. Together, these results yield reusable design rules and datasets for engineering protein-based motion.

3 Outcomes and Impact

The HFSP project itself initiated a broader undertaking that continuously yielded valuable scientific results and only recently culminated in a breakthrough that has significantly advanced a specific subfield. The insights, models, data, and components are being taken up and further developed within the team and beyond. There remains substantial scope both for the further development of molecular motors and for a deeper understanding of their mechanisms of action, as well as for the application of the knowledge gained. Beyond the lab, the project catalysed a community through recurring meetings and contributions to field-wide perspective pieces, while training a cohort of researchers who now bridge modelling, protein design and single-molecule experimentation.

The project converted the study of motors from observational to constructive, enabling rigorous tests of mechanochemical principles in simplified protein systems. This has been, and will likely remain, important for understanding these fundamental processes of life, which also occur continuously in the human body. Translational relevance is plausible in the longer term. Protein motors that guide themselves along molecular 'roads' suggest programmable nanoscale transport for synthetic cells, diagnostics or biocomputing. The Lawnmower's self-fuelled propulsion – consuming only its track – offers a compact actuation mode that could one day support targeted delivery or micro-remediation.

4 Role of HFSP and Conclusion

Investigators characterize HFSP as the only funder that would have backed the project in its high-risk form at inception. In this way, HFSP laid the foundation for a long-term undertaking that ultimately achieved a highly significant scientific advance, whose downstream benefits remain uncertain. The funded researchers highlighted the positive impact HFSP had on the project and their careers, enabling them to work in an internationally collaborative and interdisciplinary manner, which otherwise would have been hard or impossible to achieve. In addition, the researchers highlighted the value of the low administrative burden imposed by HFSP and the community interactions HFSP enabled. This example illustrates how HFSP enables high-risk basic research that lays the foundation for later scientific breakthroughs. It also shows that, even if objectives are not achieved within the project period, a project can nonetheless be successful in the long term.

5 Sources

Baker Lab (2022). De novo designed protein rotary assemblies demonstrating designed moving parts (Science/related).

HFSP Journal (2009). Tumbleweed: ligand-gated three-legged protein walker stepping on DNA tracks; modular design concept.

IEEE/Engineering Proceedings (2015). Lawnmower design principles and Brownian dynamics rules for enzymatic burnt-bridge ratchets.

Korosec, C. S. et al. (2024). Peptide-powered protein 'Lawnmower' achieves autonomous motion on peptide lawns; microscopy trajectories and guided transport. Nature Communications (open access).

Perspective (2024). Roadmap for artificial molecular motors positioning protein motors with DNA and small-molecule devices. Nano Futures.

The Scientist (2024). 'Revving Up a Protein Lawnmower': accessible explainer and expert commentary on protein motors.

SynBioBeta (2024). 'Peptide-Powered Protein Lawnmower...': outreach piece linking potential medical and biocomputing applications.