Nanomechanical Diagnostics

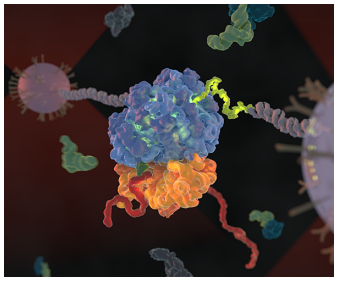
Martin Hegner
Trinity College Dublin
SFI Award (15/IA/3023)

THE CHALLENGE

Ribosomes are tiny molecular machines that are central to the decoding and translation of nucleic acids information (messenger RNA) into polypeptides and proteins. For a protein to function correctly, a folded specific three-dimensional structure is essential. Understanding protein synthesis on a single-molecule level is of particular interest to the life sciences and relevant for various diseases. How proteins fold natively with efficient fidelity while being synthesized remains largely unexplored.
Can we measure protein translation in real time at the level of one molecular machine?

THE RESPONSE

We developed a laser tweezers, single-molecule assay that provides deeper insight into the actions of a ribosomal machine at molecular level. We measured the mechanics of synthesis and simultaneous folding of the nascent polypeptide chain in real time. This enables us to deal with biological problems on a completely quantitative level. We discovered that co-translational folding occurs at predictable locations, exerting forces on the nascent polypeptide. Thus, the rate of synthesis is inherently coupled to co-translational folding, assuring reliable and fast native folding.



THE ENGAGEMENT

To achieve our ambitious objectives, we optimized our competence in designing and developing state-of-the-art diagnostic platforms by teaming up with international experts in the field of ribosomal translation. Having access to procedures that enabled specific modifications of the ribosomal motor, allowed tricky experiments to be performed. These academic alliances allowed us to maximise our research outcomes.

THE IMPACT

As a result of better molecular level understanding, we can now directly measure how this process occurs in a protein called hTau40 that is directly involved in Alzheimer's disease. Patients with neurodegenerative diseases such as Alzheimer's and Parkinson's may gain deeper insight of how their condition is triggered by misfolded proteins, and ultimately be able to avail of new treatments. The study also will allow researchers to survey and alter the expression of proteins that are difficult to produce with pin-point accuracy.
Apart from strengthening Ireland's international reputation in Bio-Nanoscience, the research on ribosomal translation has been covered by several leading news outlets, among them *Nature Index* that promotes annual international research highlights at national level.

THE NEXT STEPS

Understanding the molecular interaction of microRNA, anticancer drugs and other antibiotic effectors during ribosomal translation will allow their effect on nascent proteins at the single molecule level to be further investigated. The efficacy of antibiotics can be tested one by one in real-time. The direct insight into protein folding modulated by drugs will elucidate the origin or treatment of diseases.