Speeding up and slowing down: altering translation speed to enhance protein yield

The challenge
One way to increase the yield of recombinant proteins is to increase the speed of translation, through the use of DNA sequences containing codons that are frequently used in the host genome – a process known as codon optimisation. But codon optimisation might reduce activity activity, for example by producing poorly folded protein, especially for proteins that are difficult to express.

Project aims
This study aimed to investigate if rhythmically alternating slow and fast protein synthesis might improve that activity of a lead to a novel format antibody, by allowing it to fold correctly.

The partnership
Tobias von der Haar, from the University of Kent has developed computer software that models translation and can be used to design DNA sequences that are translated quickly. This was used to design two codon-optimised fast sequences, as well as a rhythmic sequence, in which slowly decoded regions were introduced between defined codon-optimised antibody domains.

The industrial partner, UCB Celltech, synthesised the DNA sequences, cloned them into CHO cells and then analysed expression levels of the antibody.

Key results
Expression of DNA constructs that were fully codon optimised reduced expression of the antibody compared a non-codon optimised DNA construct used by UCB. “This is consistent with the current theory that rapid translation, which normally maximises expression levels, can be counterproductive for difficult to express proteins,” explains Tobias.

Expression levels of the antibody encoded by the rhythmic constructs was comparable to that of the UCB construct, supporting the idea that introducing regions of slower translation can help optimise expression levels in multi-domain proteins.

However, the rhythmic construct did not increase expression levels above those obtained by the UCB construct “This indicates that the main limitation in expression levels for this particular antibody is not at the level of translation, but downstream of this – likely molecule assembly in the ER and/ or secretion,” says Tobias.

Moving forward
The data from this work has provided a starting point for a more systematic exploration of rhythm-based codon optimisation, including the optimal location of slowly translated sequences within the antibody folded domains.

In addition, analysis is currently underway to ascertain whether the introduction of slowly decoded regions has impacted the quality of the expressed antibody – based on levels of aggregated material and antibody. “If the quality of the expressed antibody has been improved, it provides a great opportunity for us to impact our processes,” says Paul Stephens of UCB.

“This was a unique opportunity to gain exposure to the kind of problems encountered in industry when trying to produce novel molecules.”