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Optimizing soluble expression of an anti-VEGF biosimilar to Brolucizumab for the treatment of age-related macular degeneration

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Statement of the problem: Age-related Macular Degeneration (AMD) is the most common cause of severe visual impairment, or blindness worldwide. It is estimated that as many as 77 million people in Europe will be affected by the disease by 2050. Neovascular AMD (nAMD), the third leading cause of blindness, is a condition caused by the overgrowth of blood vessels in the retina as a consequence of agin. As a strategy for maintaining or improving visual acuity, treatment for nAMD focuses on inhibiting angiogenesis and vascular leakage. Therapies based on anti-vascular endothelial growth factor (VEGF) essentially work by blocking the activity of VEGF, the factor accountable for the excessive growth of blood vessels in the retina. Brolucizumab has been developed as a humanised, single-chain fragment of a monoclonal antibody (scFv) designed to block VEGF-A and reduce neovascularisation and vascular permeability.

Methodology and Theoretical Orientation: Due to the reductive nature of the bacterial cytoplasm, a well-folded, functional recombinant protein may be difficult to obtain. Using the CyDisCo system resolves this situation by pre-expressing a sulfhydryl oxidase and a disulfide isomerase, thus allowing for correct protein folding and function. In this study, the gene sequence coding for the Brolucizumab's biosimilar of interest was cloned into pET-24d(+) and codon- optimized by Genscript. The plasmid harboring the biosimilar protein was co- transformed with the CyDisCo expression vector pMJS205 into E. coli BL-21(DE3) cells and subjected to dual antibiotic screening.

Findings: The maximal yeild of soluble protein expression was achieved under 0.5mM IPTG induction in M9 culture medium, after 16 h at 30°C and 220 rpm. The highest amount of soluble protein fraction was extracted in lysis buffer containing 50 mM Tris–HCl pH=8, 1 mM EDTA and PMSF, per gram of cell pellet. Adding different NaCl concentrations to the lysis buffer showed that eliminating NaCl resulted in more soluble protein isolation.

Conclusion and Significance: The CyDisCo system could be promising in producing active, accurately disulfide- bonded soluble proteins in *E. coli* cytoplasm.

Biography

Mohadeseh Haji Abdolvahab received her PhD at Pharmaceutical science from Utrecht University in 2016. After PhD, she continues her research as a Postdoctoral researcher at Radboud UMC. She worked at International pharmaceutical companies i.e. MSD and Amgen as a Biological Critical Reagent specialist and OC scientist, respectively. Then, she came back to Iran and started her new challenge as an assistant professor at Motamed Cancer Institute in Tehran, Iran. She is currently the head of Recombinant Protein Department. She is expert in the field of biotechnology, pharmaceutical sciences and immunogenicity. Her knowledge and experiences have led to the establishment of FartakTeb start-up company to facilitate commercialization of her and co-workers research. She is also the executive manager of ACCEZON, a biotech-accelerator, and the coach of several start-ups.

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