Receptor Targeting Nanobodies: Locking the Door for All MERS-CoV Mutations as a Novel Therapeutic Approach

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The MERS-CoV is a critical public health concern due to its infectious nature, severe symptoms and high fatality rate, with 36% of MERS-CoV cases resulting in death. This highlights the urgent need to develop therapeutic antibody solutions to combat the ongoing MERS-CoV epidemic. Anti-MERS-CoV neutralizing antibodies are not effective in neutralizing MERS-CoV due to the consistent mutations resulting in neutralization-escaping variants, which presents a significant gap in tackling the MERS-CoV epidemic. This project proposes an innovative approach to block MERS-CoV viral infection, by targeting the gateway receptor of MERS-CoV, named dipeptidyl peptidase 4 (DPP4) receptor. This approach employs monoclonal nanobody (Nb) Fc-fusion proteins to specifically block DPP4 receptors and inherently prevent the entry of all MERS-CoV variants. Using Artificial Intelligence-derived antibody CDR dissection and analysis algorithms, five Nbs with different attributes and key amino acid sequences were designed through in silico docking, 3-Dimensional homology, and local energy minimization. The resultant Nbs were produced in our lab and their neutralization capacity was tested through multiple in vitro assays including MERS-CoV pseudovirus Micro-Neutralization Test and cell-based binding assays. Our results demonstrated that four out of the five anti-DPP4 Nbs' designs were able to successfully bind to DPP4 and inherently inhibit MERS-CoV pseudotyped virus, with one candidate (Nb-212) showing the highest readings in all validation assays. These results support the utility of 3D-designed receptor-targeting nanobody Fc-fusion proteins to develop a universal immunotherapy to combat MERS-CoV infection, despite the mutable nature of the virus.