De Novo Nanobody Design With Neural Networks, AlphaFold, and Docking Algorithms

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Purpose: COVID-19 has killed more than 5.6 million. Nanobodies that retain the binding affinity of antibodies despite being onetenth the size, are emerging as viable treatment options to counter the mushrooming viral variants. However, discovering effective nanobodies remains a time consuming process, mostly involving extensive wet-lab procedures. My goal was to develop bio-computational techniques to accelerate the determination of nanobodies with higher specificity and affinity to a pathogenic target, reducing costs and time-to-market and thereby saving lives. Procedure: My unique computational approach used ensemble-stacking to develop nanobodies by sequencing the CDR-H3 region of nanobodies - sequence of amino acids in the variable binding region critical to determining specificity. In a search space of about 2020 different CDR-H3 sequences, the model predicted 50 effective sequences against an antigen target, by training on previous phage display data to accurately predict and rank the affinity of CDR-H3 sequences. Results: Ensemble-stacking achieved highly accurate predictions of binding affinity, with R^2 of 0.75 and a Pearson correlation coefficient of 0.87 in addition to a classification AUROC of 0.965. I tested the top 50 algorithm-generated nanobodies by using 3D computational methods to measure their binding affinity. My approach yielded nanobody candidates with a lower Gibbs Free energy value (a measure of stronger specificity and binding) of -10.24 kcal/mol compared to the best in vitro derived candidates (-9.65 kcal/mol). Conclusion: Results indicate that bio-computational methods using ensemble-stacking can be successfully leveraged to quickly and accurately generate nanobody candidates thereby accelerating development of successful vaccines.

Awards Won: Fourth Award of \$500 Fourth Award of \$500