

Computational Design of Next-Generation Malaria Vaccines

Mark Langowski

Malaria remains a leading infectious cause of childhood mortality in Africa. Both licensed vaccines target the *Plasmodium falciparum* circumsporozoite protein (CSP) but confer only partial, waning protection. One possible limitation is the immunogen: the immunodominant repeat region is conformationally flexible, so few elicited clones may engage the conformations recognized by potentially inhibitory antibodies. In the blood stage, reticulocyte-binding protein homolog 5 (RH5) is the most advanced target, with RH5.1 showing ~55% efficacy in a recent Phase IIb trial in children. However, RH5.1 is difficult to manufacture, aggregation has precluded nanoparticle display, and much of its surface elicits non-inhibitory antibodies. We apply deep learning-based design — RFdiffusion for motif scaffolding and ProteinMPNN for sequence design — to build immunogens displaying only inhibitory epitopes. For CSP, we scaffold the CIS43 and L9 epitopes onto rigid de novo backbones that lock their protective conformations. For RH5, we both redesign the native fold for thermostability and nanoparticle compatibility and scaffold growth-inhibitory epitopes de novo. I will present characterization showing that designs bind inhibitory antibodies with little-to-no detectable binding to non-inhibitory mAbs, that they are structurally validated to atomic resolution, and that they elicit the intended responses in rodent models. Together these define a route to improved malaria vaccine candidates.