Commentary

Searching for Achilles' heel: can rational design of malaria vaccines overcome antigenic diversity?

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Invited commentary on 'Broadly neutralizing antiviral antibodies' by Corti and Lanzavecchia

Antigenic diversity is a characteristic of many successful pathogens, giving rise to variants that can overcome pre-existing immune responses. This is a well-recognized problem for vaccine deployment, and one for which there are a number of solutions. In the case of influenza, the vaccine is reformulated every year to reflect the three most prevalent circulating strains of the virus. Pneumococcal vaccines are polyvalent (currently covering up to 23 strains) and are periodically reformulated to incorporate additional, particularly problematic, strains. However, some pathogens are so diverse, and so rapidly evolving, that this approach is simply not feasible. HIV-1 is one such pathogen and here an alternative approach has been to isolate 'broadly neutralizing' antibodies and to identify the conserved or semi-conserved epitopes to which they bind, with the aim of incorporating these into vaccines which, it is hoped, will provide immunity to many diverse strains of the virus.¹ This paradigm has now been applied to a protective, but highly polymorphic, blood stage antigen of the malaria parasite, *Plasmodium falciparum*.²

In an extremely elegant study, Dutta and colleagues² immunized animals with a mixture of four proteins representing four diverse alleles of *P. falciparum* apical membrane antigen 1 (AMA1) and observed that the resulting antibodies efficiently inhibited *in vitro* growth of parasites carrying these four alleles as well as parasites expressing 22 non-vaccine alleles. The authors hypothesized that a process analogous to 'original antigenic sin' accounted for the preponderance of antibodies recognizing conserved rather than polymorphic epitopes. The epitopes recognized by broadly neutralizing monoclonal antibodies derived from these

immunisations were mapped onto the crystal structure of AMA1 using a suite of chimaeric proteins and were found to bind to the conserved face of the molecule, close to the hydrophobic trough where AMA1 binds to its partner protein, RON2. Furthermore, the antibodies were deduced to target two distinct biological processes, namely, binding of AMA-1 to RON2, which is essential for formation of the moving junction that drives parasite invasion into the host red blood cell,³ and proteolytic processing and surface redistribution of membrane-bound AMA1.⁴

While this study raises the realistic hope that an AMA1 vaccine comprising a handful of diverse antigenic proteins might provide protection against many or most of the currently circulating AMA1 variants, the long term impact of such a strategy is perhaps less obvious. *Plasmodium* spp. parasites are not only among the most diverse of all human pathogens, but are unusual in having an absolutely obligatory sexual stage in their life cycle. Since mixed genotype infections are common, especially in highly endemic areas, genetic reassortment and recombination is the norm and the majority of new infections are genetically unique. This genetic richness, when combined with the extensive genetic bottlenecks that occur at every transmission event (only one or two of the many millions of blood stage parasites in any particular host will ever be taken up by a mosquito and transmitted), creates the perfect scenario for rapid selection and spread of advantageous mutations.⁵ The concern must surely be that a widely used and highly effective vaccine, especially one which targets the rapidly replicating red blood cell stage, will impose an immune selection pressure that (sooner rather than later) drives the emergence of 'vaccine escape' mutants. The extent to which these mutants thrive and spread within the population will depend on their fitness. In other words, a mutation in a functionally constrained portion of the molecule — such as the hydrophobic binding trough of AMA1 — may impair the viability of the parasite, but studies are now required to determine the capacity of AMA1 (and other conserved vaccine targets) to accumulate such mutations without significant loss of fitness.

References

- 1 Corti D, Lanzavecchia A. Broadly neutralizing antiviral antibodies. *Annu Rev Immunol*. 2013;31:705–42.
- 2 Dutta S, Dlugosz LS, Drew DR, Ge X, Ababacar D, Rovira YI, *et al.* Overcoming antigenic diversity by enhancing the immunogenicity of conserved epitopes on the malaria vaccine

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- candidate apical membrane antigen-1. PLoS Pathog. 2013;9(12): e1003840.
- 3 Tonkin ML, Roques M, Lamarque MH, Pugnère M, Douguet D, Crawford J, *et al.* Host cell invasion by apicomplexan parasites: insights from the structure of AMA1 with a RON2 peptide. Science. 2011;333(6041):463–7.
- 4 Dutta S, Haynes JD, Barbosa A, Ware LA, Snavely JD, Moch JK, *et al.* Mode of action of invasion-inhibitory antibodies directed against apical membrane antigen 1 of *Plasmodium falciparum*. Infect Immun. 2005;73(4):2116–22.
- 5 Mackinnon MJ, Marsh K. The selection landscape of malaria parasites. Science. 2010;328(5980):866–71.