Although these clinical results are promising, they are preliminary. The study's sample size was small and did not include a control group. Furthermore, all patients received hormone replacement therapy, which confounds the hormone-based measurement of follicle growth. Patients were also monitored monthly and were receiving clomid (a fertility drug that stimulates further follicle growth) when follicles were observed. This frequent tracking increases the risk of detection bias and the possibility that similar outcomes would be observed in a control group managed in the same way. Spontaneous pregnancies happen in ~5 to 10% of patients with POI (*10*), so without a control group and accounting for biases and confounders, it is not clear whether the outcomes reported by Lin *et al*. are clinically meaningful.

Nevertheless, the study of Lin *et al*. advances women's health by demonstrating the therapeutic potential of targeting the extrafollicular tissue to improve ovarian function. In addition to POI, ovarian fibrosis is associated with ovulatory defects, ovarian aging, ovarian cancer pathogenesis, polycystic ovarian syndrome, endometriosis, and off-target effects of chemotherapy and radiation. Robust clinical trials are needed to test the effects of antifibrotic compounds that have shown preclinical efficacy in these contexts. These trials must consider the population of women who will benefit most and the treatment regimen that maximizes ovarian function. Additionally, they should define relevant controls and the fertility and endocrine outcomes that should be measured. Targeting the ovary therapeutically is challenging because human folliculogenesis occurs over months, the ovarian reserve is constantly declining, and the safety bar for intervention is very high given that germ cells are involved. Although drug repurposing can accelerate clinical translation, identification of ovarian-specific drug targets is likely to be the most successful approach. Therefore, phenotypic assays that mimic ovarian physiology, including the stroma, are important drug-screening tools (*11*–*13*). Clinical methods to measure ovarian fibrosis in real time are also essential to monitor the efficacy of emerging therapeutics (*14, 15*). Strategies that modulate the microenvironment of the ovary to release its full fertility and endocrine potential can make the extension of ovarian longevity tangible. □

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IMMUNOLOGY

A double helix twist in HIV vaccine design

DNA origami scaffolds displaying HIV antigens stimulate focused antibody responses in mice

Oliver Bannard[1] and **Mark R. Howarth**[2]

DNA, the genetic material of life, is being increasingly appreciated as a nanoscale building material. Being programmable, rigid, and highly soluble, DNA can be designed to self-assemble into a vast range of architectures. These properties underpin the field of DNA origami, in which a long single-stranded DNA scaffold is folded into programmed shapes by oligonucleotides that connect different parts of the scaffold (*1*). On page 574 of this issue, Romanov *et al*. (*2*) demonstrate that DNA origami can be used to display human immunodeficiency virus (HIV) protein antigens. When given to mice, these nanoparticles elicited antibody responses that may pave the way for broadly protective immunity against infection. This approach could lead to more effective HIV vaccines.

HIV is a formidable challenge for vaccine development, because it evolves rapidly, integrates into the host genome, and establishes lifelong infection. Moreover, HIV's primary target for neutralization is its envelope glycoprotein (Env), which is unstable, shielded by glycan (sugar) molecules, and sparsely distributed on the viral surface (*3*). Although HIV infection triggers strong antibody responses, most of these antibodies do not block infection or they only neutralize a narrow subset of HIV variants. Nonetheless, some infected individuals eventually generate broadly neutralizing antibodies (bnAbs) that block diverse variants. Although bnAbs arise too late to prevent chronic infection, bnAbs can protect against infection with sensitive HIV variants when used prophylactically (*4*). Unfortunately, bnAbs have unusual characteristics that preclude their induction by conventional vaccination.

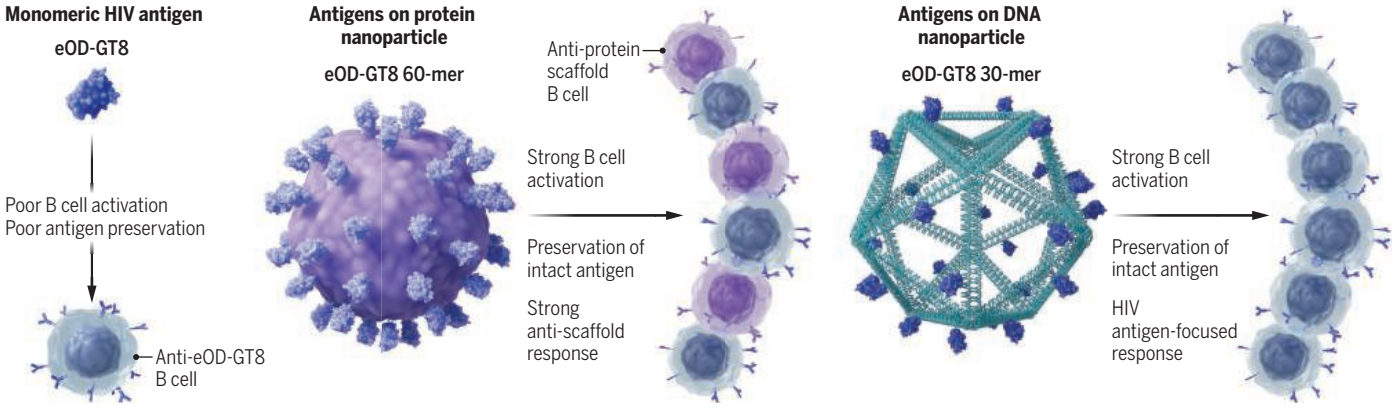
All antibodies develop from germline sequences expressed as B cell receptors (membrane-bound antibody signaling complexes that sense antigens) by naïve precursor B cells. Upon activation, antigen-specific B cells form germinal centers, where their antibodies go through affinity maturation—iterative cycles of somatic hypermutation and selection that improve antigen binding. Neutralizing activity is typically achieved with just a few mutations for most pathogens. However, HIV bnAb precursors must accumulate exceptionally high mutation loads to achieve neutralization breadth. In natural HIV infection, such maturation unfolds over years, coevolving with continually changing virus forms (*3*). Sequential immunizations with rationally designed immunogens are hoped to accelerate this process.

VRC01-class bnAbs have been a focus of research in this area because they use a VH1-2*02 heavy-chain gene, which is relatively common in human naïve B cells, paired with genes encoding a variety of light chains bearing a short CDR3 loop (*5*). Although VRC01-class germline precursors bind Env weakly, a synthetic Env immunogen, eOD-GT8, binds germline VRC01-class antibodies with high affinity and lacks most Env epitopes that trigger the production of non-neutralizing antibodies (*6*). eOD-GT8 evokes a poor immune response as a monomer, but fusion to a protein scaffold that self-assembles into 60-mer nanoparticles overcomes this limitation (see the figure). Multimeric antigens are far more immunogenic than monomeric antigens because their repetitive architecture cross-links multiple B cell receptors, enhances antigen uptake for presentation to T cells, and promotes antigen deposition and retention within B cell follicles, where germinal centers form (*7*, *8*).

Herein lies a dilemma: The very protein scaffolds that confer high

Vaccine engineering to produce focused antibody responses against HIV antigens

The HIV antigen eOD-GT8 is engineered to bind strongly to B cell receptors that can mature and promote broad protection to HIV. However, eOD-GT8 is poor at activating B cell responses on its own (left). Displaying 60 copies of eOD-GT8 on a protein nanoparticle enhances B cell activation but also induces competing responses to the protein scaffold (middle). Displaying 30 copies of eOD-GT8 on a DNA nanoparticle focuses antibody responses toward the HIV antigen (right). Subsequent immunizations will aim to guide B cells to mature and express broadly neutralizing antibodies against HIV.



immunogenicity to eOD-GT8 introduce competing epitopes that divert immune responses from the desired target. Selection of B cells during affinity maturation is based on how well they bind to and acquire antigen tethered to the membranes of follicular dendritic cells. The B cells then process and present the antigen on major histocompatibility class II (MHC class II) membrane-bound complexes to helper T cells, which are limiting in number. Thus, germinal center B cells that recognize a given immunogen compete for a shared pool of T cell help, including B cells specific for eOD-GT8 and the protein scaffold. Moreover, complex protein structures sometimes display additional competing B cell epitopes from intermolecular interfaces, or resulting from posttranslational modifications or loss of native structure (*9*). An ideal scaffold for displaying antigen would be nonproteinaceous but retain stiffness and programmable size and shape—criteria that DNA fulfills (*10*–*12*).

Romanov *et al.* initially immunized mice with 40-nm-diameter DNA virus-like particles displaying 30 eOD-GT8 units. These particles elicited only small germinal center responses that were comparable to those observed after immunization with monomeric eOD-GT8. Although rapid degradation of scaffold DNA by serum nucleases could have explained the weak response, similar outcomes in mice lacking most serum endonuclease activity prompted deeper investigation. The authors found that N-linked glycans on eOD-GT8, which are sugar chains sensed by the innate immune system, were too widely spaced on the 30-mer DNA virus-like particles to allow bridging by mannose-binding lectin, which activates the complement system. Therefore, antigen capture by complement receptor–expressing follicular dendritic cells was inefficient, likely reducing the quantity of antigen available to B cells. By refining the DNA origami design to reduce interantigen spacing, Romanov *et al.* increased glycan density, improved mannose-binding lectin engagement, and focused the germinal center response to favor the formation of HIV antigen-binding B cells. This observation may be explained by the very low activity of extracellular protease enzymes within B cell follicles (*13*). This environment preserves the native structure of antigens that arrive promptly to follicles, thereby restricting exposure of competing epitopes that would otherwise be revealed through denaturation.

Because DNA virus-like particles lack scaffold-derived peptide epitopes that would be recognized by T cells, they triggered modest antibody responses in immunized mice. However, fusing eOD-GT8 with a peptide that binds well to most MHCII complexes partially overcame this limitation. The resulting DNA virus–like particle generated smaller germinal centers than protein nanoparticles, but more antigen-specific B cells owing to superior germinal center focusing. This construct was also more effective in promoting responses from B cells expressing VH1-2*02 and bearing light chains with short CDR3 regions—a prerequisite for VRC01-class bnAb development.

Romanov *et al.* provide compelling proof of principle that DNA-based architectures can overcome otherwise unfavorable features of immune responses. Further studies are needed to establish scalability, safety, and cost-effectiveness of DNA origami vaccines. Once biological efficacy is established, transformative gains in production efficiency may follow, as demand for HIV therapeutics drove the massive scale-up of solid-phase peptide synthesis (*14*).

As Romanov *et al.* also acknowledge, DNA-based immunization has potential to induce the production of anti-DNA antibodies (*10*, *15*), which might be particularly risky for people predisposed to autoimmunity (who have overreactive immune systems). Anti-DNA responses were not observed by the authors, but this possibility warrants further evaluation with animals genetically or environmentally predisposed to generating antibodies against DNA. Future work should also decipher the optimal combination of antigen structures and vaccination types to elicit mature bnAbs and sustain their high titers. Achieving widely protective HIV immunity may also require the generation of multiple antibody lineages and use of complementary immunological mechanisms relying on additional sophisticated immunogen designs. However, even before clinical testing, research into DNA virus-like particle vaccines has already revealed fundamental immunological principles that will inform rational design of future vaccines. □

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