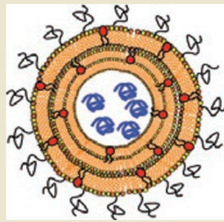
Cross-linked multilammelar vesicles



Subunit vaccines seldom activate the potent T-cell responses needed to counteract many viral diseases and cancers because of inefficient presentation of antigens to naive $CD8^+$ T cells. Success to date in encapsulating antigens and adjuvants within unilamellar and multilamellar lipid vesicles is thought to arise from an enhancement of antigen stability and the mimicking of cues normally associated with a protective immune response. Moon *et al*. build on these efforts by covalently crosslinking the concentric membrane bilayers that encapsulate a core filled with model antigen ovalbumin (blue in picture) and embedding the lipid-like Toll-like receptor 4 (TLR4) agonist monophosphoryl lipid A (MPLA; red in picture) within the bilayers. Comparisons with simple liposomes and multilamellar liposomes of the same lipid composition reveal that the new polyethylene glycol–decorated, interbilayer–crosslinked multilamellar vesicles (ICMVs) elicit T-cell and antibody responses to the model antigen ovalbumin in mice comparable to those for strong, live-vector vaccines. Stapling of the bilayers appears to prolong persistence of the vaccine in the serum while optimizing vaccine delivery to antigen-presenting cells. It remains to be seen whether these promising effects will translate to better protective immunity in disease models. (*Nat. Mater.* **10**, 243–251, 2011) *PH*

Immunity through IL-17

Pediatric *Streptococcus pneumoniae* infections represent a significant health problem, despite the existence of effective vaccines. Vaccines cover only a fraction of the extant serotypes, and the population of *S. pneumoniae* colonizing the nasal mucosa is dynamic, necessitating the production of new vaccines. Moffitt *et al.* use a genomic approach to design serotype-independent vaccines that trigger immune responses in mouse models and in human cells. Based on prior work showing that mucosal-derived immunity in adults resistant to *S. pneumoniae* is mediated by IL-17–secreting $CD4^+$ T cells, the researchers first screened a library of pneumococcal proteins for those that stimulate IL-17 secretion *in vitro*. They identified 17 proteins that were present in all 22 of the sequenced *S. pneumoniae* genomes and did not cross-react with human or other bacterial proteins. From those, five that were expressed at high levels in *Escherichia coli* were selected for further testing. Two selected proteins (both components of transport systems) stimulated mouse splenocytes and human peripheral blood monocytes to secrete IL-17. In addition, mice immunized intranasally with those antigens were protected from infection with clinical strains of *S. pneumoniae*; this protection was abrogated by depleting the animals of $CD4^+$ T cells or by inhibiting the IL-17 pathway. The work identifies a new route to immunity as well as a novel set of antigens—none of the antigens overlaps with those that elicit antibody responses. In addition, this approach may be applicable to other mucosal pathogens, of which several exist in humans. (*Cell Host Microbe* **9**, 158–165, 2011) *LD*

RNAi phenotyping in trypanosomes

Although the genome of *Trypanosoma brucei,* the parasite that causes African sleeping sickness, has been sequenced, <10% of the ~7,500 protein-coding genes have been studied systematically by genetic disruption. Alsford *et al.* describe an RNA interference (RNAi)-based, genome-scale approach to phenotyping genes. Using their method, thousands of genes—many previously unannotated—are identified as essential for normal growth in one or more stages of the parasite lifecycle. The approach relies on first creating a library of *T. brucei* cells in which the expression of different regions of the genome are suppressed by an RNAi cassette. In contrast to previous approaches requiring one-by-one construction of vectors that target specific genes, the cassettes express double-stranded RNA transcribed from random fragments of genomic DNA, enabling targeting of >99% of all protein-coding sequences in the genome. Once the cells are grown under conditions of interest, next-generation sequencing is used to identify cassettes containing genes whose knockdown causes cells to grow slowly or not at all. Genes required for parasite growth in conditions that model a human host are potential drug targets. (*Genome Res.* published online, doi:10.1101/gr.115089.110, 1 March 2011) *CM*

Antimalarial fungal pesticide

Entomopathogenic fungi like *Metarhizium anisopliae* have been proposed as promising alternatives to chemical pesticides for controlling a range of insect pests. An issue with using unmodified *M. anisopliae* to control malaria is that it takes as long for the fungus to kill mosquitoes as the time needed for the malarial parasite to complete its life cycle. Therefore, unless the fungus infects the mosquito at the beginning of the parasite life cycle, the mosquito can still spread malaria before it dies. Strategies to accelerate the killing process have been reported (*Nat. Biotechnol.* **25**, 1455–1456, 2007). However, these strategies would likely select for fungal resistance if most mosquitoes are killed before they reproduce. Fang *et al.* address this challenge by engineering *M. anisopliae* to express proteins that block development of the malarial parasite within mosquitoes. Expression of a fusion protein results in 98% clearance of parasites from infected insects, while eliminating the requirement that fungal and parasite infection coincide. Containing the host range of widely disseminated *M. anisopliae* spores remains a potential obstacle to implementation of this biocontrol strategy. Gao *et al.* recently presented a comparative genomic analysis of *M. anisoplae* and *Metarhizium acridum,* a relative with a more restrictive host range. The insights from such approaches may be invaluable in efforts to refine the approach. (*Science* **331**, 1074–1077, 2011; *PLoS Genet.* **7**, e1001264, 2011) *PH*

Mutational load in iPSCs

Safety is a preeminent requirement in any clinical application of induced pluripotent stem cells (iPSCs). Two new studies of the genetic stability of iPSCs may raise some cause for concern. Gore *et al.* sequenced most of the protein-coding regions of 22 human iPSC lines and searched for point mutations, small insertions and deletions, and alternative splicing variants. Each exome had on average six mutations, about half of which were not detected in the progenitor fibroblast lines and must therefore have arisen during cell culture or the reprogramming process itself. In the second study, Hussein *et al.* analyzed copy number variations in 22 human iPSC lines, their progenitor fibroblasts and 17 human embryonic stem cell lines. Early-passage iPSCs had substantially more mutations than late-passage iPSCs or the control cell types, although these mutations did not seem to provide a selective advantage and largely disappeared with passaging. More research is needed to understand the mechanisms underlying the mutational load in iPSCs and their implications for the safety of iPSC-based therapies. (*Nature* **471**, 63–67; 58–62, 2011). *KA*

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