couplings[5] — an explanation of the relative powers of the strong, weak, electromagnetic and gravitational forces — remains as a firm, reasonably quantitative motivation for supersymmetry.

We are unlikely to see notable, qualitatively new results from the LHC in the immediate future because the machine will be out of commission for at least a year while it is upgraded to allow higher collisional energy and luminosity. The second-generation LHC will empower greater accuracy in all the checks of minimalism, and possibly finally deliver supersymmetry — or an unanticipated surprise! ■

Frank Wilczek *is in the Center for Theoretical Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA.*
e-mail: wilczek@mit.edu

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HIV

Roadmaps to a vaccine

More than 30 years since the AIDS pandemic began, there is still no effective vaccine. But analysis of broadly acting, potent human antibodies obtained from single cells suggests a rational approach to vaccine development. SEE ARTICLE P.469

HUGO MOUQUET & MICHEL C. NUSSENZWEIG

Our understanding of how humans respond to HIV has been revolutionized by the introduction of techniques for isolating anti-viral antibodies from single cells[1]. Such methods have led to the discovery of naturally occurring, potent antibodies that can neutralize a broad range of HIV viruses, and prevent[2] and suppress[3] infection. These findings, combined with the association between antibody responses and protection from infection that was identified in a human trial[4] of the vaccine RV144, have reinvigorated the quest for antibody-based HIV vaccines. However, it has also become clear that anti-HIV antibodies undergo unusually high levels of mutation[1,5], which represents a potential stumbling block for vaccine development. Among four recent studies[6–9] that address this subject is a paper in this issue, in which Liao *et al.*[9] (page 469) track antibody and viral evolution during one patient's response to HIV*.

Antibodies are produced by the B lymphocytes of the immune system. The receptors on the surface of each circulating B cell are unique, enabling an immune response to any foreign structure. When a B cell encounters an entity that matches its receptor, it is stimulated to proliferate and secrete antibodies against that structure. Although B-cell genes frequently undergo somatic (non-germline) mutation to increase the affinity of the antibodies they produce, anti-HIV antibodies are unusual in that they are highly somatically mutated — they are therefore quite different from those encoded by the B cells that initially respond to the infection[1,10]. Furthermore, these mutations seem to be required for the antibodies to bind to heterologous viral-envelope proteins (those expressed on most HIV viruses)[5,10]. If B cells that express the germline antibody precursor do not bind to the antigen, how are they stimulated in the first place, and why do the antibodies need so many mutations? Answering these questions is of fundamental importance in attempts to reproduce this antibody-development process by vaccination.

Some patients with HIV develop broadly neutralizing antibody activity, but only 2–4 years after infection. Scrutiny of the antibodies produced by single human B cells[1] showed that these broadly neutralizing responses are due to a combination of antibodies in some individuals, and to single, potent antibodies in others[2]. In an attempt to dissect the natural pathways that lead to the generation of these antibodies, Liao *et al.* studied a patient who developed broad and potent antibodies.

The authors investigated the co-evolution of the HIV-1 virus and the broadly neutralizing antibodies for 34 months from the start of the infection. They isolated a virus-specific antibody named CH103, and clonal variants of it, from single memory B cells that were obtained using a fluorescently tagged viral-envelope protein as bait[3,5,11]. CH103 neutralizes 55% of HIV-1 isolates and targets the site on the virus that binds to CD4 molecules on the surface of T cells (the immune cells that HIV infects). Like other antibodies in this class[5,11], CH103 is highly somatically mutated, and its unmutated germline precursor fails to bind to heterologous HIV-1 envelope proteins[9].

One of Liao and colleagues' key findings is that the germline precursor antibody of CH103 has high affinity for the envelope protein expressed by the founder virus that infected the individual. The authors suggest that a progenitor B cell that expresses this germline antibody might only be stimulated to respond if it is presented with the envelope proteins of the founder virus, or similar proteins. The idea that certain envelope proteins are more likely to induce broadly neutralizing antibodies is supported by experiments in macaques showing that specific envelopes induce such responses to simian HIV, whereas others do not[12].

However, simply initiating the antibody response is not sufficient for effective immune defence. It takes time and unusually large numbers of somatic mutations for antibody breadth and potency to develop. Liao *et al.* reconstructed the CH103 clonal lineage by using samples that went back to the time of infection. Although all members of the lineage recognized and neutralized the founder virus, the affinity and neutralizing activity against heterologous viruses gradually increased through the accumulation of somatic mutations. The authors also found that, as previously described for glycan-dependent broadly neutralizing antibodies[13], viral diversification and the emergence of 'escape mutants' (those with mutations in the site targeted by the antibody) preceded the development of antibody breadth. By studying a crystal structure of the CH103 antibody in complex with its envelope protein target, Liao *et al.* showed that HIV escapes antibody pressure by mutating amino-acid residues in and around the CD4 binding site. These resistant viruses then elicit further somatic mutation and 'affinity maturation' of CH103 antibody variants, resulting in greater neutralization breadth of the antibody response.

"These data suggest a molecular explanation for why broadly neutralizing anti-HIV antibodies take 2–4 years to develop."

The reason for the high level of somatic mutation required to produce broadly acting, potent anti-HIV antibodies has recently been investigated[6]. Under normal circumstances, high affinity of an antibody for its target is usually achieved after the accumulation of 10–15 mutations in the complementarity-determining region of the antibody that forms the antigen contact site. However, broad and

*This article and the paper under discussion[9] were published online on 3 April 2013.

potent anti-HIV antibodies contain 40–100 somatic mutations[1,5,6,11] that span both the complementarity-determining region and the relatively constant, and mutation-resistant, framework regions. Experiments in which mutations in the framework regions were selectively reverted showed that these mutations are necessary for the evolution of broad and potent anti-HIV antibodies[6]. These structural alterations in the antibody were found to contribute to direct contacts with the virus and to enhanced flexibility of the antibody structure, both of which are required for optimal breadth and potency.

Combined with Liao and colleagues' findings, these data suggest a molecular explanation for why broadly neutralizing anti-HIV antibodies take 2–4 years to develop. Moreover, they indicate that an effective vaccine may require shepherding of B-cell responses through multiple rounds of the natural antibody maturation and mutation process, using naturally derived viral envelopes that induce the production of broad and potent antibodies in people with HIV. A recently suggested[7,8] alternative, non-mutually exclusive approach is to design specific 'immunogen' molecules that would bind to and activate B cells that produce the germline precursors of broadly neutralizing antibodies. Whether such roadmaps can be used to design effective vaccine strategies has yet to be determined, but they present a strong and testable route to addressing the main challenges of creating an antibody-based HIV-1 vaccine. ■

Hugo Mouquet *and* **Michel C. Nussenzweig**
are at the Rockefeller University and the Howard Hughes Medical Institute, New York, New York 10065, USA.
e-mails: hmouquet@rockefeller.edu; nussen@rockefeller.edu

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IMAGING

Magnetic bacteria on a diamond plate

A new approach has been used to image magnetic fields in living cells of magnetotactic bacteria. The technique could be applied to study the dynamics of magnetism in other biological systems. SEE LETTER P.486

MIHÁLY PÓSFAI &
RAFAL E. DUNIN-BORKOWSKI

Just as schoolchildren sprinkle iron filings on a sheet of paper placed over a magnet to visualize the magnetic field around the magnet, scientists who are interested in magnetism strive to image the magnetic fields within and around objects across a wide range of spatial and temporal scales. Although many different magnetic imaging techniques are now available, imaging micro- and nanoscale magnetic fields in living organisms is still challenging. On page 486 of this issue, Le Sage *et al.*[1] describe an advanced optical magnetic imaging technique which they use to study the three-dimensional magnetic fields that originate from chains of magnetic nanocrystals inside the living cells of magnetotactic bacteria.

Many organisms contain magnetic nanocrystals inside their bodies; some use them to navigate in magnetic fields, whereas others use them to harden or protect their tissues. Magnetotactic bacteria are the simplest organisms that are known to contain magnetic nanocrystals. Their delicate internal chains of tailor-made iron oxide or iron sulphide particles have attracted intense scientific interest since their discovery[2], and are often used as nanoscale natural laboratories to develop and test magnetic imaging techniques[3–6].

The fundamental principles of the technique that Le Sage *et al.* use have been known for some time[7] and have been applied to map magnetic-field variations on the nanoscale[8,9]. They involve detecting changes in the quantum spin states of crystallographic defects called nitrogen–vacancy centres in a diamond chip (a nitrogen atom and a vacancy substitute for two neighbouring carbon atoms in the diamond crystal lattice). The novelty of the authors' study lies in using this approach to image magnetic fields in living microorganisms.

"The study opens up the possibility of dynamic imaging of the development of magnetic fields in bacteria as their chains of magnetic crystals grow."

When the authors placed magnetotactic bacteria on a diamond surface, they found that the cells' magnetic fields affected characteristic signals, known as electron spin resonance frequencies, of the nitrogen–vacancy centres in the diamond. They detected such signals using an optical beam, and reconstructed all vector components of the magnetic field created by the chains of magnetic nanocrystals in the cells. Le Sage and colleagues' experimental set-up allowed them to simultaneously acquire magnetic maps and optical images of the bacteria. In this way, they could compare the recorded magnetic fields with the positions of the cells, map the positions of the chains of magnetic nanoparticles (see Fig. 4 of the paper[1]) and quantify the magnetic moments of the chains.

The importance of the technique for studying biomagnetic structures lies in the fact that both magnetic and optical images can be collected with a spatial resolution of about 400 nanometres from a population of cells across a wide field of view — spanning 100 μm × 30 μm. Although other approaches provide better spatial resolution for imaging magnetic fields in bacteria[3,5,10], at present these methods cannot be used under ambient conditions and for imaging multiple cells across such a large field of view in real time. Le Sage and colleagues' study opens up the possibility of dynamic imaging of the development of magnetic fields in bacteria as their chains of magnetic crystals grow.

Another potential application would be to screen non-magnetic mutant bacteria produced in genetic-engineering studies aimed at understanding the biological mechanisms that control the growth of magnetic nanocrystals inside cells[11]. The sharing of magnetic nanoparticles between daughter cells during cell division could also be studied. In addition to understanding magnetic nanocrystal formation by bacteria, it may be possible to use the method to reveal the presence and evolution of putative magnetic structures in the tissues of more complex organisms, including insects, birds and humans, under ambient conditions.

Some words of caution are warranted before making excessively bold predictions about