hinders phagosome maturation in macrophages through a process that does not require ESAT-6 or other known substrates secreted by this system[10]. Taken together, these data indicate that ESX-1 modulates innate immune responses of the infected host through several mechanisms, which probably involve ESX-1-mediated secretion of ESAT-6 and other unidentified factors.

Raghavan and colleagues[2] identify a previously unknown component of ESX-1 that is not only a central regulator of it but is also secreted by this system. They find that, in *M. tuberculosis*, the *Rv3849* gene — which is located some distance from the main ESX-1 gene cluster surrounding the *esxBA* operon — is required for ESX-1 function. The protein product of *Rv3849*, EspR, is highly similar to a gene transcription factor of the harmless soil bacterium *Bacillus subtilis*. The authors find that EspR is also a DNA-binding transcriptional regulator — *Rv3849* deactivation leads to changes in the transcription of a few operons in the *M. tuberculosis* genome, including the *Rv3616c–3612c* cluster, which encodes at least two ESX-1-secreted proteins and is required for the functioning of ESX-1[11] (Fig. 1).

Although it is not surprising that mycobacteria express a transcription factor that regulates the expression of ESX-1 components, that EspR is itself secreted by ESX-1 is an unexpected result. The authors propose that secretion of this protein constitutes an unusual feedback loop that could be part of a finely tuned control process to prevent excessive or prolonged activity of ESX-1 during infection of mammalian cells. Although secretion of a regulatory protein as a mechanism for diminishing its activity inside the cell has been described before, EspR might represent the first example of a transcription factor that is actively exported from the cell by the same secretion system that it induces.

One can imagine how EspR could impose a limit on the level and duration of ESX-1 activity. When initially expressed, this protein could be essential for activating ESX-1 to secrete high levels of virulence-promoting proteins, thus allowing *M. tuberculosis* to establish its infection in the host. Once infection is achieved, secretion of EspR might lead to a reduction of its transcriptional activity within the bacterium and diminished ESX-1 activity. This would partially attenuate virulence, thus favouring either bacterial persistence or a slow, chronic infection in order to enhance transmission.

Can EspR production be turned on or off, and — if so — what external stimuli and bacterial sensing and signalling molecules could be responsible for this? Are other components of the ESX-1 system separately regulated by factors distinct from EspR? These questions, together with the identification of other secreted ESX-1 substrates and their mechanisms of action in mammalian host cells, should provide many opportunities for deciphering the unique logic of mycobacterial virulence strategies.

It will also be interesting to determine whether EspR has any specific function once it has been exported from the bacterial cell. Because at least two other ESX-1 secreted products — ESAT-6 and CFP-10 — are major targets for the immune response, it is possible that EspR is also a prominent mycobacterial antigen. If so, this could have implications for the development of new vaccines and diagnostic tools for tuberculosis. ■

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OPTICS

Electronic eyeballs

Takao Someya

The ability to fabricate silicon optoelectronic devices on a curved surface will lead to imaging systems with exceptional characteristics. This innovative technology will find diverse applications.

All animals have curved imagers for their eyes. By contrast, artificial vision systems such as digital and video cameras have to rely on flat image-recording surfaces. These artificial imagers are made with silicon microfabrication technologies to produce the necessary network of semiconductor photodetectors, and they can now create pictures with more than ten million pixels. But there remains the big problem of producing bright, distortion-free images with a flat imager. Given the distortion that occurs at the edges of lenses, multiple combinations of different lenses are required for effective imaging. Consequently, lens arrangements are heavy, expensive and produce darker results than they would otherwise do[1].

On page 748 of this issue, Rogers and colleagues (Ko *et al.*)[2] describe how they have drawn inspiration from animals' eyes and have succeeded in eliminating these fundamental limitations of conventional artificial-vision systems. Their electronic eye camera (Fig. 1) is based on silicon electronics that is designed to have full mechanical compressibility–stretchability, meaning that it can be moulded onto a hemispherical substrate.

The authors' method is outlined in Figure 1 of their paper (page 749). It depends on two main advances. The first is the fabrication, on a silicon wafer, of a network of semiconductor photodetectors that can tolerate elastic compressibility despite being subjected to high levels of strain (typically exceeding 50%). The crucial features that allow such compressibility are the thin metallic wires that interconnect the photodetectors. The second innovation is the use of elastomeric elements that can transform a photodetector network initially made in a planar configuration into hemispherical

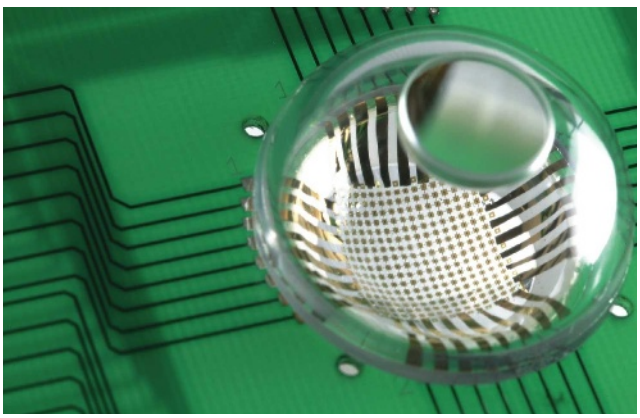

Figure 1 | The electronic eye camera. This device shows the integration of the concave photodetector system devised by Ko *et al.*[2] into a miniature camera that has a single, simple lens. Apart from the lens at the top, the hemispherical cap would not normally be transparent. The camera is about 2 centimetres in diameter. (Photo courtesy of J. A. Rogers.)

shapes for implementation in imagers. This technology heralds the advent of new classes of imaging devices with wide-angle fields of view, low distortion and compact size.

The recent developments[3] in compressible–stretchable electronics provide the prospect of many new applications such as long-term bionic implants, robotic sensory skins[4], ambient displays embedded in (for example) wallpaper, and intelligent surfaces that are chemically or electronically functionalized and can interact with people, objects or their environment. One of the most difficult requirements is to achieve excellent mechanical robustness and good electronic performance while satisfying basic electrical requirements — the materials and circuit architecture used in conformable and stretchable electronics must be designed such that their mechanical integrity and electrical functionality are preserved during the fabrication and use of the resulting products. In recent years, Rogers and his colleagues[5] have developed one- and two-dimensional stretchable ribbons and circuits for this purpose; the two-dimensional compressible components used in the electronic eye camera represent a natural extension of this line of research.

The promise of this technology extends well beyond the hemispheric configuration demonstrated by Ko *et al.*[2]. For instance, it could be applied to integrate optoelectronics onto complex, curvilinear surfaces for use in health-monitoring devices that optically detect concentrations of oxygen and other constituents in blood. The new possibilities in optics design should lead to a further reduction in the imaging distortion of ultra-compact camera systems in which photodetector surface geometries can be carefully optimized. Furthermore, distortion-free, adaptive focusing mechanisms might be feasible if the stretchable imager of these camera systems can be developed on actively deformable substrate surfaces. Such simplified systems should have much improved optical transparency — that is, have much reduced optical loss compared with that arising from the use of multiple lenses. This beneficial feature will not only generate more industrial applications for these systems, it will also benefit fundamental research at wavelengths for which existing materials cannot ensure sufficient optical transparency.

In addition to the further development of concave photodetector systems, we can expect to see advances in creating convex imagers — for use in, for example, artificial insect-like compound eyes with exceptional dynamic visual acuity, and in fish eyes that have a 360° field of view. These and other types of biologically inspired device should become feasible given the advances in optical engineering made possible by the advent of geometrically transformable and stretchable–compressible electronics and optoelectronics. All in all, with their electronic eye camera, Rogers and colleagues have delivered an outstanding contribution by showing how progress in electronics can be made by overcoming the constraints of flat silicon wafers. ■

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PHARMACOLOGY

Unready for action

Joe Henry Steinbach

Boy scouts recognize that the key to success is to be prepared. The same is true of molecules that bind to and open ion channels — the least effective ones are slower to prepare the channel to be ready for opening.

Some drugs, known collectively as agonists, can be thought of as molecular switches — if the molecule fits the active site of the receptor, the biological response is switched on. But so-called partial agonists pose a problem for this simple model. A partial agonist is a compound that elicits less than a full biological response on binding to its target, even when it occupies all the available binding sites. How can this be?

Reporting on page 722 of this issue, Lape *et al.*[1] provide an answer for partial agonists that bind to two structurally related channels — the glycine receptor and the muscle nicotinic receptor. The binding of a full agonist to these receptors causes the channels to be open almost constantly, so that the maximum possible current in the channel is observed as ions flow through. But when partial agonists bind, the channel is open for a smaller proportion of the time, and only a fraction of the maximum current flows. Lape *et al.* show that this is because the partial agonists often fail to trigger a conformational change in the receptor that precedes the actual opening of the channel.

The classic view of drug action is known as the occupancy model, and proposes that, when a drug binds to an effector (a receptor or an enzyme), the drug–effector complex constitutes the signal that generates a biological effect (Fig. 1a). The discovery of partial agonists posed a problem for this simple model, so an additional step was added[2]: binding creates an inert drug–effector complex, which then undergoes a conformational change to yield an active state. In this scheme, partial agonists binding to ion-channel receptors were thought to cause those channels to open slowly (Fig. 1b). This idea has dominated thinking about the nature of partial agonism for the past 50 years.

But a third model for receptor activation has also been proposed, in which an intermediate state exists between the initial, inert drug–effector complex and the receptor with the channel open (Fig. 1c). This intervening state has been called the flip state[3]. Readers of a military bent might prefer to think of it as a cocked state.

The flip-state theory certainly makes sense for ion channels. These large proteins consist of several subunits, and their activation involves a considerable conformational change that probably takes place in a series of steps. Thermodynamic analyses of kinetic experiments have been used to infer the relative times at which individual amino acids in muscle nicotinic acetylcholine receptors are perturbed during activation[4,5]. The results suggest that five distinct sets of residues exist, with those near the agonist binding site moving first, and those near the channel's gate moving later. This kind of analysis has also been used to compare a range of molecules that bind to acetylcholine receptors, from weak partial agonists to full agonists[6]. The differences between agonists appeared near the start of the activation process, at the same time as the movements of amino acids close to the agonist binding site.

The best way to study receptor states as agonists bind is by the kinetic analysis of currents through a single ion channel. Lape *et al.*[1] adopted this approach, analysing the actions of partial agonists using high-resolution, single-channel recordings. They examined the durations of the brief periods in which a channel is closed while an agonist or a partial agonist is bound, and confirm the existence of a flip state. Their results also show why partial agonists fail to maximally activate these ion channels. It seems that partial agonists do not have an intrinsically low channel-opening rate. In fact, they are just as good at opening channels as full agonists — that is, the rate of conversion of the flip state to the open state is as high as for full agonists. The difference is that partial agonists are ineffective at converting the inert drug–receptor complex to the flip state, so their overall ability to produce open channels is low.

It would be grand to know what the flip state looks like. Crystallography can provide satisfying pictures of proteins, although it can be difficult to relate the resulting static images to