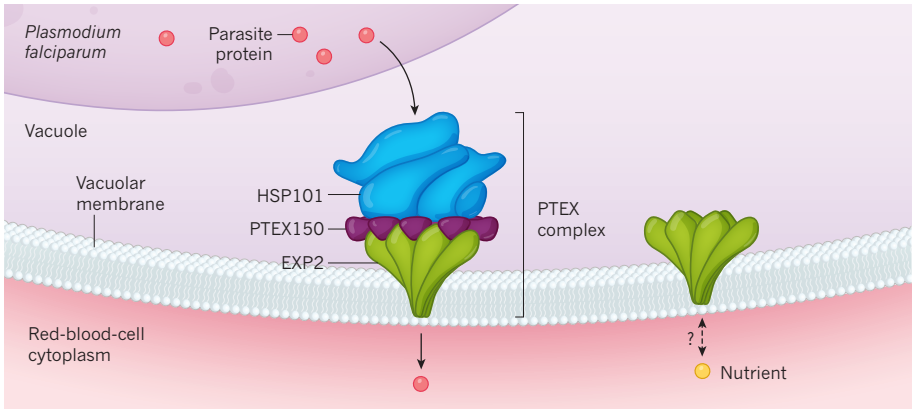

Figure 1 | Proteins that are essential for the malaria parasite's survival. During part of its life cycle, the *Plasmodium falciparum* parasite resides inside a membrane-bound vacuole in human red blood cells. Ho *et al.*[2] report the structure of a parasitic multiprotein complex called PTEX, which is present on the inside of the vacuolar membrane. This complex is essential for parasite survival, and proteins are exported from the vacuole through PTEX into the cytoplasm of red blood cells. The authors' analysis provides a detailed view of three of the proteins that form PTEX: EXP2, HSP101 and PTEX150 (only 20% of the structure of PTEX150 was determined). The authors' work also illuminates how proteins transit through the PTEX complex. Garten *et al.*[4] report that EXP2 can form a channel that enables nutrients to be transported across the vacuolar membrane. Whether this occurs in both directions, or in only one, is not known.

novelty offers few clues to how it functions. EXP2 synthesized in the laboratory can form protein channels in lipid bilayers[9]. However, there have been no reports of full-length HSP101 or PTEX150 having been successfully synthesized for use in *in vitro* experiments. This has prevented structural analysis of the proteins, or reconstitution of the core PTEX complex in lipid membranes, to determine how the complex assembles and functions.

Because of these experimental limitations, Ho *et al.*[2] opted instead to extract PTEX directly from red blood cells containing the parasite. Then, using a technique called cryo-electron microscopy (cryo-EM), the authors captured two distinct structural conformations of the core PTEX complex in the process of exporting unfolded protein cargo — they called these conformations the 'engaged' and 'resetting' states. The cryo-EM analysis revealed that HSP101, PTEX150 and EXP2 assemble into an asymmetrical structure containing six molecules of HSP101, seven of PTEX150 and seven of EXP2. These structures closely align with models of the organization and size of PTEX that had been predicted from biochemical and protein-analysis experiments[3,5].

Ho and colleagues found that the seven EXP2 molecules, which make up the protein channel in the lipid membrane, create a funnel shape, with the amino terminus of each molecule forming a transmembrane helix in the vacuolar membrane to provide an anchoring 'stem' (Fig. 1). The 'mouth' of EXP2 constitutes the bulk of the protein, and faces into the vacuole. This end of EXP2 contains a domain that tethers it to the carboxy-terminal domain of HSP101, situated directly on top. Only approximately 20% of the structure of PTEX150 could be determined. Nevertheless, this was sufficient to reveal that each PTEX150 molecule slots in between adjacent EXP2 molecules at the mouth of the EXP2 funnel, curling down towards the stem. Thus, PTEX150 provides a protective path for unfolded protein cargo transiting from HSP101 to EXP2.

Of the three proteins, HSP101 displayed the greatest structural difference between the engaged and resetting states of PTEX, and on this basis the authors propose a mechanism for how cargo is threaded through PTEX's central cavity. In this model, domains of the six assembled HSP101 molecules form two 'hands' that work together to thread unfolded cargo through the PTEX150 and EXP2 funnel. In the engaged state of PTEX, both the 'active' and 'passive' hands of HSP101 grasp the unfolded cargo. The cargo is then fed downwards through the central cavity of PTEX in a spiral fashion as it passes from the active to the passive hand. In the resetting state, HSP101's active hand moves upwards to grasp the next section of the cargo protein for transport, and the passive hand grips the cargo to prevent it from slipping backwards and away from the PTEX channel.

The cryo-EM structures provide insight into several crucial interactions between the PTEX components. These interactions are potentially required for assembly and optimal function of the complex, and could be tested using genetic approaches to validate the model. Ho and colleagues were unable to determine the structure of the N-terminal domain of HSP101 that binds the protein cargo. Thus, it is unclear how cargo is recognized by HSP101, and whether cargo proteins are unfolded by proteins known as chaperones before they reach PTEX. Given that unfolded proteins pass through PTEX, these cargo proteins would then need to be refolded to function, presumably by other chaperone proteins. However, because EXP2 does not

50 Years Ago

Everybody knows, of course, that there is a genuine and unavoidable conflict between the functions of museums as centres of scholarship and as places of entertainment. Curators can be forgiven for wishing that visitors would let them get on with serious work. In practice, the Science Museum seems to have mastered these yearnings quite successfully, and in the past few months there have been some welcome signs of an anxiety to please … Yet there is a long way to go before the museum shoulders wholeheartedly its responsibility for seeing that people, and particularly young people, are provided with a vivid and contemporary vision of what science is like. Even the new children's exhibition will not let the little creatures know about electronic computers, for example.

From *Nature* 7 September 1968

100 Years Ago

Considerable interest was taken last week in the demonstrations of "reading by ear" at the British Scientific Products Exhibition. The original construction of Dr. Fournier d'Albe's "type-reading optophone" … has recently been modified by replacing the Nernst lamp by a small drawn-wire lamp, and by arranging the whole apparatus in such a manner that any ordinary book or newspaper can be inserted and read without cutting it up into pages or columns. The demonstrations consisted in taking an ordinary book … , opening it at random … and asking the blind pupil to read a few words or lines … By a curious coincidence the first words thus read were "in the light". The reader, a girl of nineteen blind from early infancy, was the first blind person to read by ear.

From *Nature* 5 September 1918