the light-detecting fibre varies according to the person's heart rate[4]. This physiological application of textiles could be used in primary-care settings.

Rein and colleagues' results pave the way for integrating low-cost electronic components into fabrics. Wearable lasers and light detectors and the ability to communicate through garments are some of the possibilities opened up by this work. A strength of the study is the use of high-performance devices that are already available, as opposed to previously reported competing materials and components based on compounds known as chalcogenides[5] that are still far from reaching the market.

This work describes only the initial phases of the technique, and much optimization remains to be done. One key step in the fabrication procedure is the mounting of the chips in the preform, which at present is done manually. A mechanized approach could take the technology to a higher level of reproducibility and maturity.

As is the case in many fields, whether or not the technology will enter the market will probably be dictated by economic rather than scientific factors. Nevertheless, practical applications of the fabrics can already be envisaged. Although a high-quality communication link will probably find fierce competition from available technologies, one might more readily expect to see the fabrics used for a hospital bed sheet to monitor a patient's physiological state, or for a glowing flag in a football stadium. ■

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PARASITOLOGY

Drug candidate and target for leishmaniasis

Better treatments are needed for the neglected tropical disease leishmaniasis. The development of a compound that tackles the disease in mice, and the identification of the protein it targets, offer a way forward. SEE ARTICLE P.192

CAROLINA M. C. CATTA-PRETA & JEREMY C. MOTTRAM

The parasite-mediated disease visceral leishmaniasis is prevalent in the tropics and causes 20,000–40,000 deaths across the globe each year[1]. The drug treatments currently used for this condition have substantial side effects, are difficult to administer and can result in the evolution of treatment-resistant parasite strains. On page 192, Wyllie *et al.*[2] present studies of a series of related drug-candidate molecules that are being developed for leishmaniasis treatment. They also identify the target of the most promising compound.

It is more than 100 years[3] since drugs based on the chemical element antimony[4] were first used to treat visceral leishmaniasis, also known as black fever or kala-azar. This sandfly-transmitted disease is caused by the protozoan parasites *Leishmania donovani* in the Old World and *Leishmania infantum* in both the Old World and the New World. Antimony-based drugs are still used today as part of a small range of treatments for the condition. In 2012, the World Health Organization reviewed[5] the global impact of neglected tropical diseases in the developing world and identified the control of leishmaniasis worldwide and its elimination on the Indian subcontinent as priority targets. To achieve these goals, methods are needed to identify compounds with potent anti-parasitic activity that are suitable for safe and effective therapies.

Parasites from the *Leishmania* genus live and replicate inside a membrane-bound vacuole in macrophage cells of the immune system. Wyllie and colleagues studied compounds called pyrazolopyrimidines, which are effective against a related protozoan parasite, *Trypanosoma brucei*. The authors optimized the compounds by assessing their effect on *in vitro* infection of macrophages by *Leishmania* and by testing them using a mouse model of visceral leishmaniasis. They selected one named compound 7 as the best candidate for additional study because it had a good safety profile, high potency and suitable properties for development as an orally administered drug. However, the compound's mode of action was unknown, so the authors sought to identify its molecular target in the parasite. Such target identification is important because it can aid the assessment of possible off-target effects in humans, as well as the likelihood of the emergence of drug resistance.

The authors used a biochemical approach to find proteins that bind to compound 7, and identified three enzymes of interest: CRK3, CRK6 and CRK12. These are similar to cyclin-dependent kinases (CDKs), protein kinases that need to bind a cyclin regulatory protein to enable their kinase activity[6]. When the authors

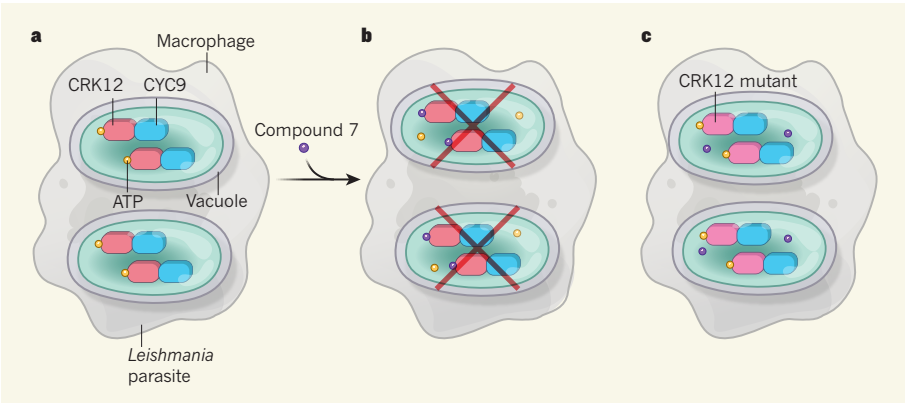

Figure 1 | How a drug candidate targets the *Leishmania* parasite. Wyllie *et al.*[2] have identified candidate drug molecules for treating the tropical disease leishmaniasis, which they tested in mouse models of the disease. The most promising molecule is called compound 7. **a**, The protozoan *Leishmania* parasite causes leishmaniasis. It infects host immune cells called macrophages and resides in a membrane-bound vacuole. The authors identified the protein kinase enzyme CRK12 as a target of compound 7. This enzyme is similar to cyclin-dependent kinases, has a binding pocket for the molecule ATP and is found in complex with the cyclin protein CYC9. **b**, The level of parasites in mice treated with compound 7 was reduced. The authors' computational modelling studies indicate that compound 7 binds in the ATP-binding pocket of CRK12, thus preventing ATP binding and inhibiting the enzyme's activity, leading to parasite death. **c**, The authors identified a mutation in the catalytic domain of CRK12 that was associated with drug resistance that arose in a laboratory setting. When *Leishmania* parasites were engineered to express this mutant version of CRK12, the effectiveness of compound 7 was reduced. It seems reasonable to speculate that the mutation alters the binding affinity of compound 7 to CRK12, but not that of ATP.

isolated the enzymes, they were found to be associated with cyclin partners. CDKs regulate cell-cycle progression and are key anticancer drug targets[6].

Wyllie and colleagues investigated parasites that had developed resistance to pyrazolopyrimidine compounds that was caused by exposing parasites to these molecules in the laboratory. The authors carried out whole-genome DNA sequencing to determine how this drug resistance had arisen. These results focused attention on CRK12, together with its associated cyclin protein CYC9, as the probable target of compound 7. This focus was supported by their finding that parasites that express both CRK12 and CYC9 at higher than usual levels have increased resistance to the effects of compound 7. Moreover, the authors identified a mutation in the CRK12 gene in drug-resistant parasites; when this mutation was introduced into wild-type parasites, they became resistant to compound 7 (Fig. 1). The authors' computational modelling studies indicate that compound 7 binds CRK12 in the pocket where the molecule ATP usually binds.

Although CRK12 in complex with CYC9 seems to be the primary molecular target of compound 7, it is possible that other kinases in *Leishmania* could be inhibited by the molecule and contribute to its anti-parasitic activity. The range of protein kinases in *Leishmania* is different from that in humans, so this study provides an impetus to search for other 'druggable' protein kinases in the parasite[7]. Methods such as gene editing[8] using the CRISPR–Cas9 technique have improved researchers' ability to perform large-scale genetic validation of drug targets in *Leishmania*. However, a major bottleneck in the drug-discovery process for neglected tropical diseases is the identification of highly specific chemical probes that allow chemical validation — evidence that confirms the molecular target of a compound of interest.

The genetic and chemical validation of CRK12 as the target of pyrazolopyrimidines is a key advance because it opens further avenues of exploration for drug discovery. If the pyrazolopyrimidines ultimately fail to be suitable for clinical use, other compounds that inhibit CRK12 could be developed. There have been only a few drug-discovery efforts targeting enzymes in *Leishmania*[9], mainly because not many targets have been genetically or chemically validated. In this instance, a target-based approach would require the production of CRK12 in complex with CYC9, and the development of an enzyme assay that would be suitable for high-throughput screening to test libraries of chemical compounds. Protein kinases are generally amenable to such approaches, but Wyllie and colleagues report that this has proved challenging so far for CRK12.

Further research should be carried out to investigate the regulation and function of the CRK12–CYC9 complex in *Leishmania* to determine whether modifications such as phosphorylation regulate the activity of the complex. One key question is why is this complex essential for the survival of *Leishmania* in its mammalian host? The authors found that compound 7 disrupts the parasite's normal cell cycle, which is consistent with the known function of CDKs in cell division. However, the details of the molecular mechanisms at work here remain to be elucidated.

A study[10] in 2016 identified the triazolopyrimidine molecule GNF6702 as having potent activity against *Leishmania*. It acts by inhibiting the cell's proteasomal protein-degradation machinery. Thus, in the past few years, two promising compounds with known targets have emerged. Furthermore, collaborations between pharmaceutical companies, academic institutions and the non-profit Drugs for Neglected Diseases Initiative have identified an increasing number of candidate molecules for leishmaniasis treatment that could be orally administered; these might progress from preclinical studies to clinical trials (see go.nature.com/2lc3mgn).

Is it time to consider testing such chemicals in combination with each other? Combination therapy for visceral leishmaniasis is being evaluated for current drugs because this approach increases treatment efficacy, reduces treatment duration and limits or delays the emergence of drug resistance[11]. The use of lower concentrations of the compounds and shorter treatment times might help to avoid the emergence of difficult-to-treat *Leishmania* strains, such as those that have arisen after treatment with the drug miltefosine[12]. Wyllie and colleagues' work might open the door for a new drug to be developed. Yet the attrition rate for drug candidates is high. More drug candidates therefore need to be identified to increase the chance that treatments for visceral leishmaniasis will make it to the clinic. ■

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ALZHEIMER'S DISEASE

Lymphatic waste disposal in the brain

The discovery that a set of lymphatic vessels interacts with blood vessels to remove toxic waste products from the brain has implications for cognition, ageing and disorders such as Alzheimer's disease. SEE ARTICLE P.185

MELANIE D. SWEENEY & BERISLAV V. ZLOKOVIC

A network of lymphatic vessels acts in tandem with the blood vasculature to regulate fluid balance in the body[1]. The brain does not have its own lymphatic network, but the cellular membranes around the brain, known as the meninges, do have a network of lymphatic vessels. This meningeal lymphatic system was first found[2] in 1787 and has been 'rediscovered' this decade[3–5]. Do the meningeal lymphatics have a role in brain diseases, as systemic lymphatic vessels do in systemic diseases such as cancer[1]? On page 185, Da Mesquita *et al.*[6] show that meningeal lymphatic vessels help to maintain both cognitive function and the proper levels of proteins in brain fluids (a process called proteostasis). The finding has implications for normal ageing and disorders such as Alzheimer's disease.

In the body, lymphatic vessels drain tissues of interstitial fluid (ISF), which contains waste products such as cellular debris and toxic molecules. The ISF forms a protein-rich fluid called lymph that circulates through the lymphatic system back to the circulating blood[1]. On its way, lymph is filtered through the lymph nodes, which can initiate immune responses if foreign particles are detected.

The brain does not have its own lymphatic vessels. As such, proteins and waste from the main body of the brain (the parenchyma) are transported within ISF along the walls of blood vessels to reach the cerebrospinal fluid (CSF), which circulates through the meninges[7]. It is well established that proteins, metabolic waste products and other molecules in these fluids can