# news

to the areas of release, whereas anandamide moves farther away'. These differences provide 'a one–two punch', comments Piomelli.

The results left Piomelli with questions about the individual roles of the two endocannabinoids. He speculates, '2-AG may act as a fast modulator, followed by longer-lasting and more far-reaching actions of anandamide', perhaps even corresponding to the nociceptive and emotional aspects of pain, although he calls this 'pure speculation'. Mechoulam agrees that these endogenous molecules might be tethered to emotion. 'As endocannabinoids are produced in brain areas involved in emotions and are involved in physiological states like pain, appetite and stress, which heavily involve emotion', he said, 'I believe that ultimately they will be shown to be central players in this important area. How exactly', he added, 'is still beyond us. Maybe the endocannabinoids will be good tools.'

**References**


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# Battle against malaria could involve anti-HIV drugs

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Preliminary studies suggest that antiretroviral protease inhibitors (ARPIs) could be useful in the prophylaxis and treatment of malaria, particularly in individuals co-infected with HIV-1. Kathy Andrews of the Queensland Institute of Medical Research (Herston, QLD, Australia) presented some of her group's results during the Medical Research Week organized by the Australian Society for Medical Research in June this year.

**A common target**

HIV protease inhibitors target an aspartic protease in HIV that has significant homology with plasmepsins that reside in the food vacuole of *Plasmodium falciparum*. 'Plasmodium aspartic proteases are now recognized as a novel drug target for future research', says Andrews. 'For scientists interested in rational drug-design of antimalarials, this finding opens another window with enormous potential', comments Vijay Sharma (Washington University Medical School, St. Louis, MO, USA). 'This finding has also generated considerable excitement and debate on mechanism(s) of action involving ARPIs in antimalarial research', he adds.

**Dual purpose**

Malaria is one of the deadliest parasitic diseases world-wide, killing over 2 million people annually. The global emergence of drug resistance is making efforts for treatment less effective. 'The literature contains several reports of antimalarial drugs having some efficacy against HIV but this is the first report of antiretrovirals being used to manage malaria', comments Frank Romanelli (University of Kentucky, Lexington, KY, USA). Romanelli notes that 'studies involving ARPIs are often limited by their high pill burdens, cost, side-effect profiles and propensity to cause drug–drug interactions'. Sharma agrees that 'although cost may be a critical determinant for making them a routine first-line choice, wide deployment of these drugs for HIV and malaria patients could be immensely beneficial in underdeveloped regions of the world'.

**Future studies**

Brian Greenwood (London School of Hygiene and Tropical Medicine, UK) predicts that identification of the exact target of ARPIs and their mode of action might allow some modified molecules to be developed as specific antimalarials. 'These could be even more powerful than the drugs currently being used to treat HIV', he says. It is possible that antiprotease ARPIs could provide some background protection against malaria for people on long-term ARPI treatment. 'However, more work is needed to determine whether blood taken from people on ARPIs at different periods after receiving treatment can inhibit parasite growth', he explains. If ARPI treatment maintains protective levels in the blood throughout a course of treatment, then it could provide a useful form for malaria chemoprophylaxis for at-risk groups. However, he warns that if blood concentrations fluctuate above and below inhibitory concentrations, then this would be a very effective way of selecting for parasite resistance and could quickly make this group of drugs unsuitable for use as a primary malaria treatment.

> '…this is the first report of antiretrovirals being used to manage malaria…'

**A natural experiment?**

'A natural experiment is already taking place in that patients living in highly malarial regions are now receiving ARPIs long-term and it would be helpful to measure the effect of this on the incidence of malaria both in individual subjects and at the population level', adds Greenwood. However, Andrews points out that in areas where *P. falciparum* is prevalent, protease inhibitors are not currently the first choice for HIV treatment. 'The NNRT [non-nucleoside reverse transcriptase] inhibitor nevirapine is commonly in use, particularly to treat pregnant women. We have found no antimalarial effect at therapeutic concentration for the HIV drug nevarapine', she reports. Greenwood also stresses that any large-scale studies would be difficult because of ethical concerns about having a non-ARPI-treated control group.




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