

potent, having a K_i of 11.3 μM for cathepsin L and selectivity over cathepsin B (no inhibition observed), cathepsin K ($K_i = 22 \mu\text{M}$), cathepsin S ($K_i > 40 \mu\text{M}$), cruzain ($K_i > 70 \mu\text{M}$) and CPB ($K_i > 60 \mu\text{M}$). The useful levels of biological potency achieved for a series of α,β -dimethyl monocyclic ketones and N-(3-oxo-hexahydrocyclopenta[b]furan-3a-yl)acylamide bicyclic ketones, which also display good levels of selectivity over related CAC1 proteinases, merits additional research to improve inhibitor potency.

- 2 Barrett, A.J. *et al.* (1998) *Handbook of Proteolytic Enzymes*. Academic Press
- 3 Watts, J. *et al.* (2004) Functionalised 2,3-dimethyl-3-aminotetrahydrofuran-4-one and N-(3-oxo-hexahydrocyclopenta[b]furan-3a-yl)acylamide based scaffolds: synthesis and cysteinyl proteinase inhibition. *Bioorg. Med. Chem.* 12, 2903–2925

Paul Edwards

paul.edwards@santhera.com



MICROBIOLOGY

An innate resistance tool against retroviruses

The mysterious function of an HIV-1 protein named Vif has recently started to be deciphered, revealing its unfriendly relationship with APOBEC, a human protein. The research opens up unexpected possibilities for anti-AIDS therapeutics, as the work of Vif in overcoming APOBEC activity is a necessary step for the virus to spread its infection.

Vif protein works by suppressing the antiviral action of APOBEC, an enzyme in the host cell that inhibits the replication of retroviruses such as HIV-1 and HBV. The research is pioneered by Ann Sheehy and Michael Malim at King's College London, who identified APOBEC by a subtractive screening [1]. They compared the DNA of human host cells able to produce new virion particles once infected with Vif mutated HIV-1 ('permissive cells') with the DNA of host cells that yielded dead particles after infection with

the same Vif strain ('unpermissive cells'). The investigators spotted APOBEC as the protective activity present only in these unpermissive cells (e.g. CD4 T lymphocytes) and liable for thwarting the infection.

To defend the host, APOBEC has to be incorporated into virions as they assemble in the infected cell; Vif not only prevents its incorporation during the packaging, but also removes APOBEC by targeting it for degradation by the proteasome.

APOBEC is a DNA-editing enzyme: it inactivates the viral genetic elements by hypermutation, because it catalyzes the deamination of deoxycytidine to deoxyuridine in DNA replication intermediates. However, this is not the only way for it to act against retroviruses. Sheehy and Malim have noticed that mutating the deaminase active site of the enzyme does not necessarily deprive APOBEC of its antiviral effect. If DNA editing is not always the way to destroy the virus, what then are APOBEC's alternative means of resistance? Understanding these mechanisms and how Vif allows HIV-1 to surmount APOBEC protection might provide exciting new routes to help defeat AIDS.

- 1 Newman, N.C.E. *et al.* (2005). Antiviral function of APOBEC3G can be dissociated from cytidine deaminase activity. *Curr. Biol.* 15, 166–170

Maria Elena Becker-barroso

elena.becker@kcl.ac.uk

DISEASE MECHANISMS

Cannabinoids inhibit atherosclerosis progression

Atherosclerosis is a chronic inflammatory disease, which leads to accumulation of lipids in arteries, plaque formation and their rupture, causing clinical events such as stroke and heart attacks. Currently, the treatment is limited to lowering patients' blood pressure and cholesterol levels. Commonly used drugs are statins, which have also been shown to have anti-inflammatory effects.

In their study recently published in *Nature*, Steffens *et al.* tried to influence the progression of atherosclerosis in ApoE-knockout mice, an animal model that develops atherosclerotic plaques upon a high cholesterol diet [2]. Cannabinoids are known to have an anti-inflammatory and immunosuppressive effect; some were shown to be therapeutically useful in preclinical studies for treatment of MS or rheumatoid arthritis. The authors tested the anti-atherosclerotic potential of THC, the major constituent of marijuana, as it has well documented immunomodulatory effects and it is also commercially available as anti-vomiting

or anorexia treatment.

When 1 mg/kg/day THC, a dosage that is supposed not to have any psychotropic effects, was delivered orally to ApoE-knockout mice on a high-cholesterol diet, the progression of atherosclerotic lesions was inhibited. THC binds to the cannabinoid receptors CB1 and CB2, the latter was shown by immunohistochemistry to be present in human and murine atherosclerotic plaques and colocalizes there with lymphocytes and macrophages. The recruitment of leucocytes into atherosclerotic lesions seems to be affected by THC, as experiments with intravital microscopy of the mesenteric microvasculature showed a reduced leukocyte adhesion. Isolation of lymphocytes from THC treated animals revealed that they have a diminished proliferation capacity and produce less interferon γ than lymphocytes from untreated animals. Macrophage chemotaxis was also inhibited by THC, which might lead to less migration of these cells into atherosclerotic lesions and thereby decrease inflammation. Steffens *et al.* could show that the THC action is most probably mediated via CB2 receptors, as the specific CB2 antagonist abolished the THC effects on atherosclerosis progression and macrophage interferon γ production.

THC was shown to suppress the inflammatory actions of lymphocytes and macrophages in atherosclerotic plaques by acting on their cannabinoid receptor CB2. Similar drugs with CB2 as specific target could be of clinical use for atherosclerosis treatment or even prevention.

- 2 Steffens, S. *et al.* (2005) Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature* 434, 782–786

Angelika Lampert

angelika.lampert@yale.edu

