

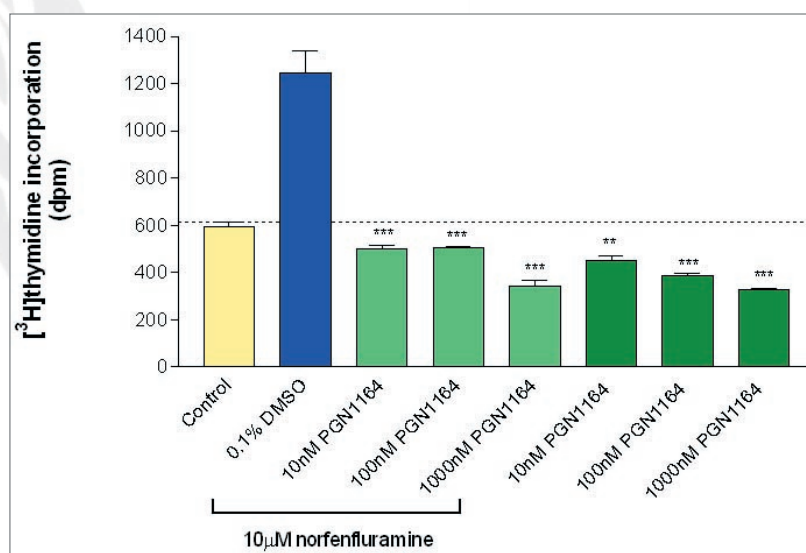
## Cardiovascular safety: heart valvulopathy

Activation of 5-HT<sub>2B</sub> receptors expressed by valvular interstitial cells (VICs) in the atrioventricular valves (bicuspid/mitral and tricuspid) of the human heart stimulates mitogenesis and is an important mechanism for drug-induced valvular heart disease (VHD). Drugs such as the withdrawn appetite suppressant fenfluramine and the dopamine receptor agonist pergolide, which are associated with heart valve fibrosis, are known to be potent 5-HT<sub>2B</sub> receptor agonists. Thus, compounds with serotonergic activity have the potential to cause valvulopathy and assessment of such liability should be an essential part of their pre-clinical drug development programmes<sup>1</sup>.

Asterand has developed an *in vitro* cell proliferation assay using cultures of human heart VICs for the evaluation of our clients' hit and lead compounds on a fee-for-service basis. VICs are isolated from fresh human heart valves and the cell population expanded in primary culture. The cells are then passaged into multi-well plates for assessment of the effects of test compounds on proliferation using a [<sup>3</sup>H] thymidine incorporation assay based on the method of Setola *et al.*<sup>2</sup>

### Features of Asterand's human VICs proliferation assay offering:

- Regular access to fresh human hearts (approximately one every week) hence just-in-time testing of newly synthesized compounds is feasible
- Robust cell isolation and expansion protocol out to P2 with VICs retaining their proliferative potential
- 48-well assay system established for parallel profiling of batches of compounds
- Rigorous assay pharmacological control - consistent stimulation of proliferation with 5-HT<sub>2B</sub> agonists that can be inhibited with 5-HT<sub>2B</sub> receptor antagonists
- Test data usually generated in 4 to 6 weeks (depending on the number of donors)
- Full reporting and analysis of assay data



The 5-HT<sub>2B</sub> agonist norfenfluramine causes proliferation of VICs in culture, which can be inhibited by Asterand's novel and selective 5-HT<sub>2B</sub> antagonist PGN1164.

<sup>1</sup> Huang, X-P. *et al.* (2009) *Mol. Pharmacol.* 76: 710-722

<sup>2</sup> Setola, V. *et al.* (2003) *Mol. Pharmacol.* 63: 1223-1229

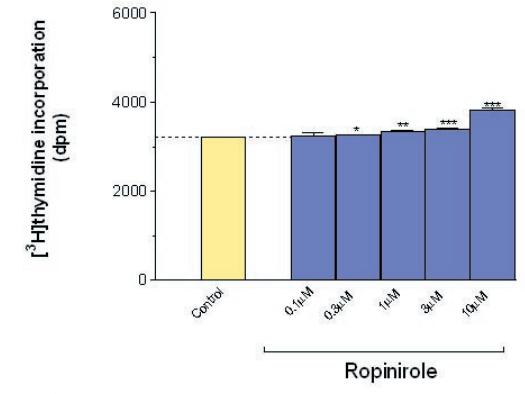
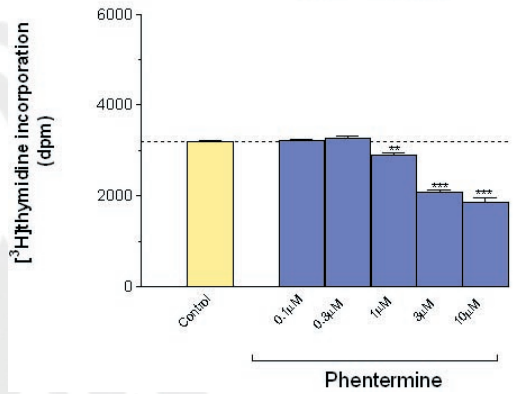
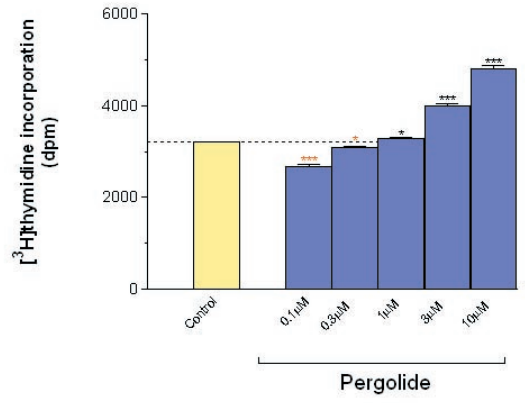
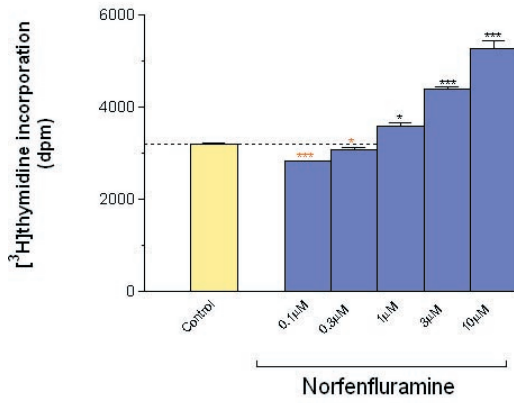
EXPERTS IN HUMAN  
TISSUE RESEARCH

EXTENSIVE HUMAN  
TISSUE NETWORK

ADVANCE PROMISING  
COMPOUNDS FASTER

INFORMED  
DECISION MAKING

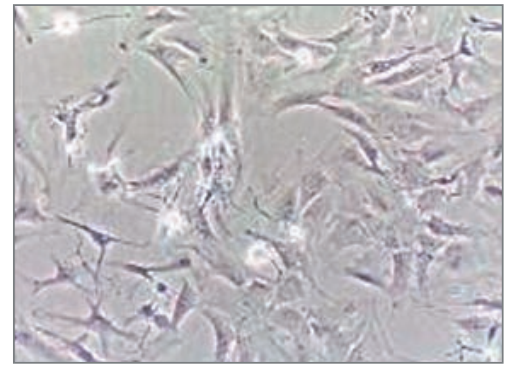
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The VICs proliferation assay can distinguish between full 5-HT<sub>2B</sub> agonists associated with VHD (norfenfluramine and pergolide) and partial 5-HT<sub>2B</sub> agonists that are not associated with VHD but cause slight stimulation of proliferation (ropinirole).



Human aortic valve leaflets



VICs after 5 days in primary culture

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