APD811, a Novel and Highly Selective Non-prostanoid IP Receptor Agonist in Smooth Muscle Cells From Patients With Pulmonary Hypertension

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Introduction

APD811 is an oral, non-prostanoid IP receptor agonist with a long plasma half-life (~ 24 hr) in development by Arena Pharmaceuticals Inc for pulmonary arterial hypertension (PAH). Little is known about the pulmonary pharmacology of this agent. We assessed the ability of APD811 to generate cyclic AMP (cAMP) and inhibit cell proliferation in pulmonary artery smooth muscle cells (PASMCs) isolated from PAH patients. The role of the IP receptor was investigated alongside prostacyclin mimetics already licensed for PAH.

Methods

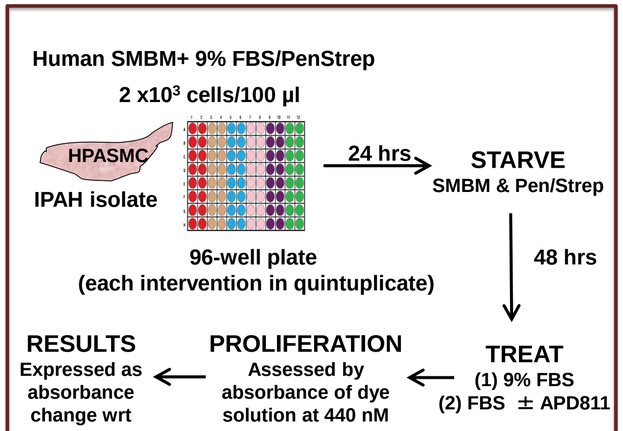

Figure 1 *Proliferation was assessed using an MTS assay in PASMCs*

Distal PASMCs were stimulated with 9% serum and treated with agonists ± RO-118452 (IP receptor antagonist; IPRA) for 1 hr or 4 days to measure cAMP (ELISA) and cell proliferation (MTS), respectively. The concentration (EC_{50}) producing the half maximal (E_{Max}) response was determined. Statistical significance was assessed by 2-way ANOVA with Bonferroni post-hoc test where *=P<0.05, **=P<0.01, ***=P<0.001.

Results

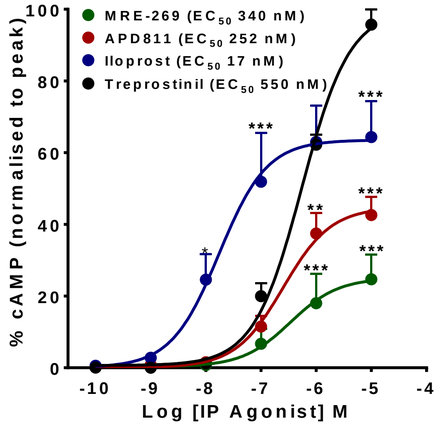

Figure 2 *Comparative concentration-response effects of the IP receptor agonists, APD811, MRE-269 (selexipag metabolite), iloprost and treprostinil on cyclic AMP levels in human PASMCs derived from 5 PAH patients (Significantly different compared to treprostinil).*

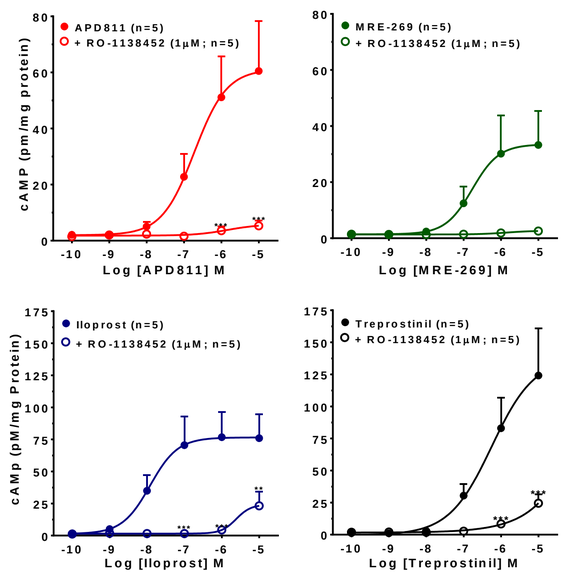

Figure 3 *Mean effect of the IP antagonist, RO-1138452 on cAMP generation induced by prostacyclin mimetics in human PASMCs from PAH patients.*

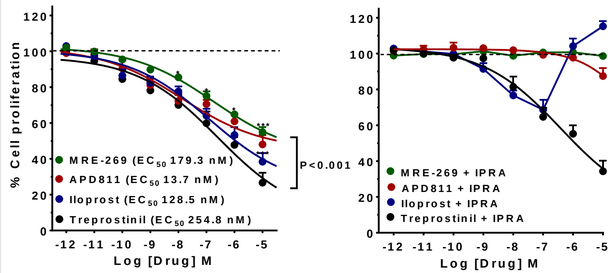

Figure 4 *Antiproliferative effects of IP agonists in human PASMCs from PAH patients: Differential effect of IP antagonist, RO-11384525 (1 µM; IPRA).*

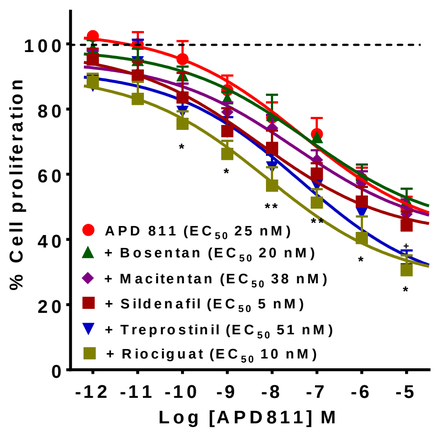

Figure 5 *Different PAH drug (100nM) combinations compared to APD811 alone (*+=P<0.05; **=P<0.01)*

Conclusion

In human PASMCs, APD811 and MRE-269 both behave as selective, but partial IP receptor agonists in cAMP and cell proliferation assays, with APD811 a more effective agonist than MRE-269. Iloprost and treprostinil inhibit proliferation through IP-receptor independent pathways. Agents stimulating cyclic GMP could work better at inhibiting cell proliferation in combination with APD-811 than endothelin receptor antagonists.

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