

# APD811 (ralinepag), a Novel Non-prostanoid IP Receptor Agonist, has Potent Antiproliferative and Vasorelaxant Properties in Human Pulmonary Artery

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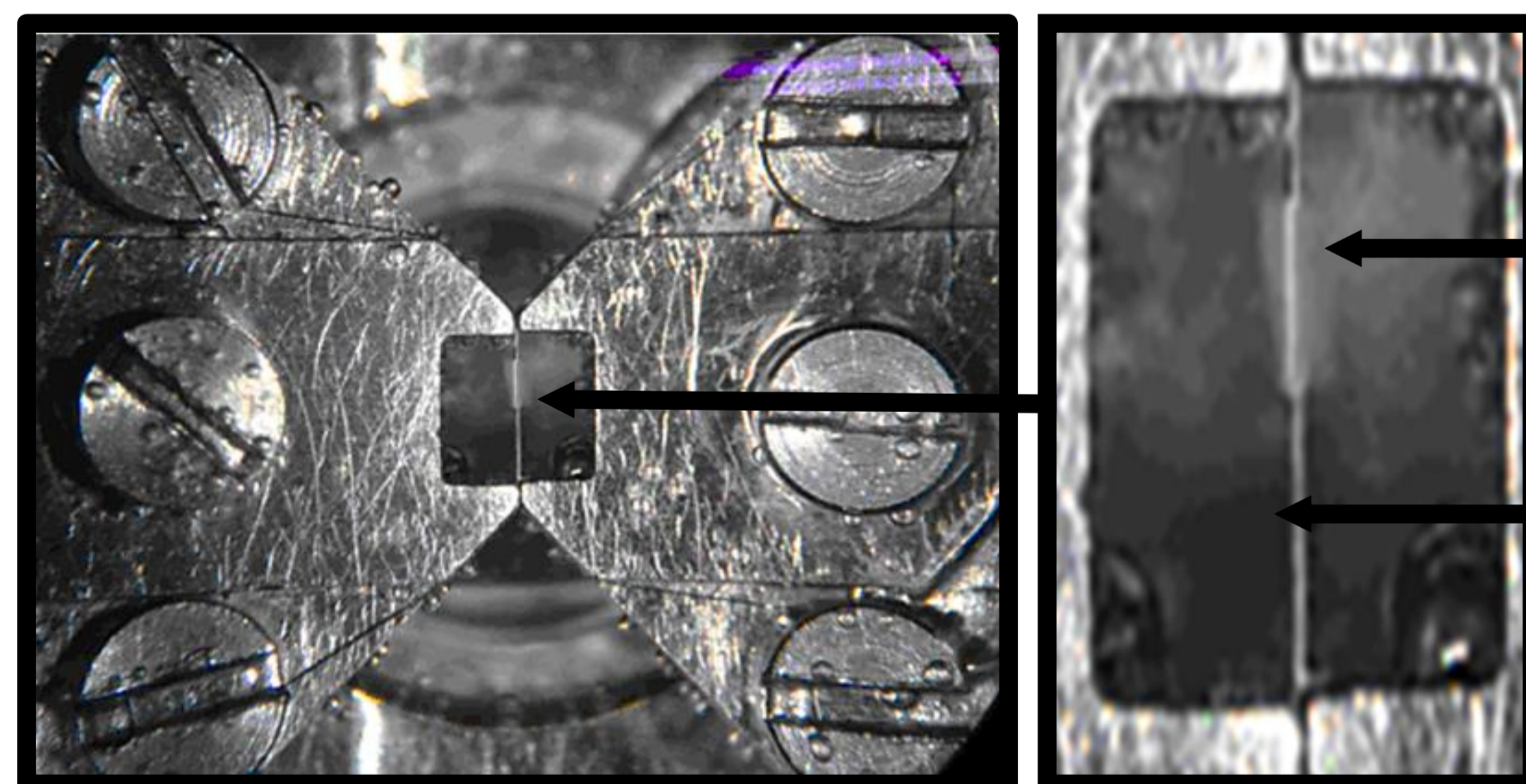
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## Purpose

APD811 (ralinepag) is a long-acting (half-life ~24hr), orally administered non-prostanoid IP receptor agonist in development for the treatment of pulmonary arterial hypertension (PAH). The aim of the study was to compare the functional effects of APD811 with other prostacyclin mimetics already licensed for PAH as well as to investigate the role of the IP receptor.

## Methods

Pulmonary arterial smooth muscle cells (PASMCs) were isolated from the lungs of patients with group 1 PAH (idiopathic or small cardiac defects). Cells were grown in 9% serum, treated with agonists ± 1 μM RO-1138452 (IP receptor antagonist) for 1 or 96hr to assess cAMP (ELISA) and cell proliferation (MTS), respectively.



Distal PA (~300 μm)  
Wire×2 (40 μm)

Figure 1. Dual-wire myography

Human pulmonary arteries (PAs) derived from histologically normal tissue of cancer patients (n=8, mean age 66yr) undergoing lobectomy were constricted with U46619 (thromboxane mimetic; 50-100nM). Endothelial functions was assessed using acetylcholine (Ach, 10μM).

The concentration (EC<sub>50</sub>) producing the half maximal response (E<sub>Max</sub>) was determined. Statistical significance was assessed by 1 or 2-way ANOVA with Bonferroni post-hoc test.

## Results

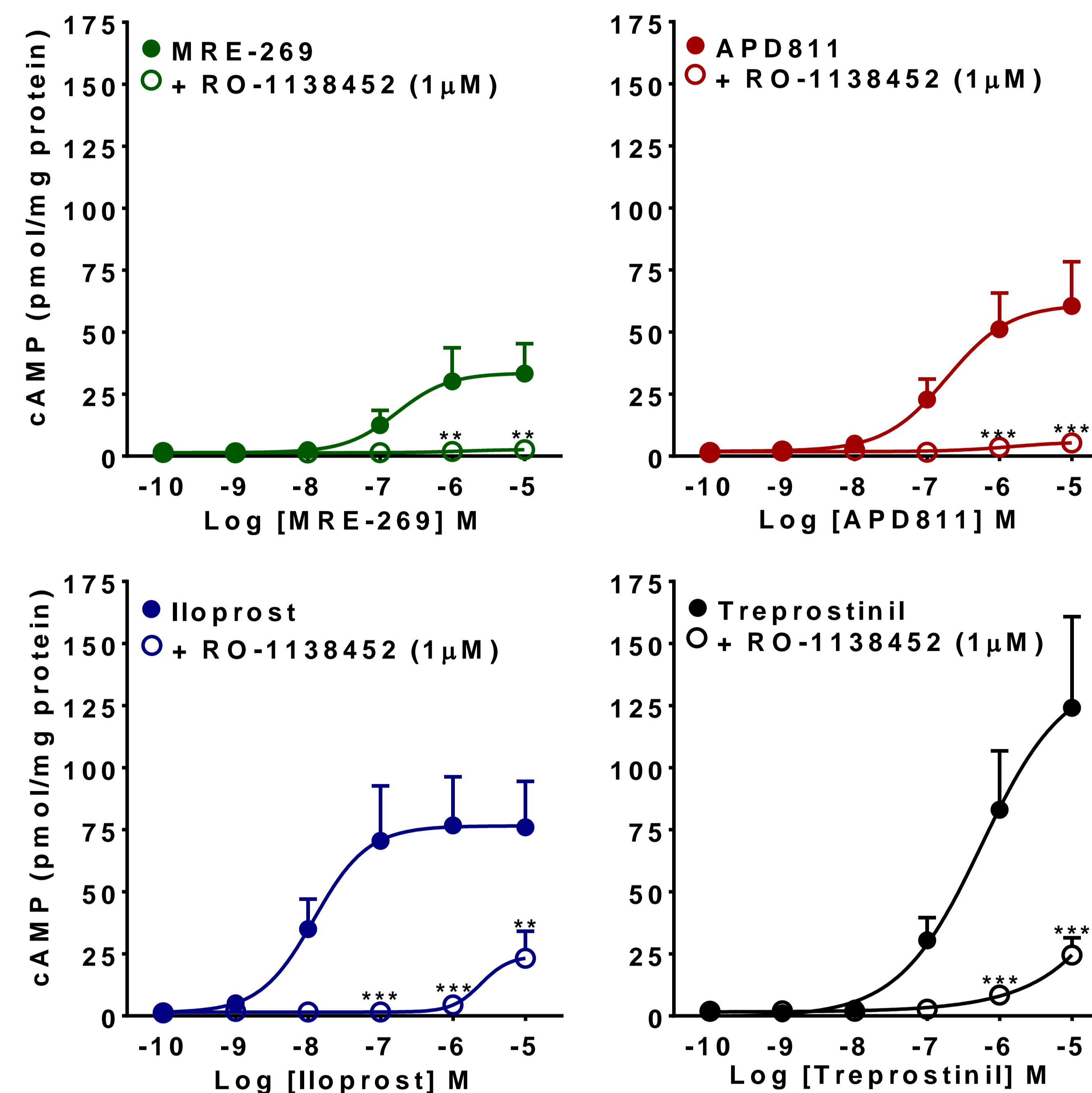


Figure 2. Concentration-dependent effects of APD811, MRE-269 (selexipag metabolite), iloprost and treprostinil on intracellular cAMP levels in PASMCs derived from PAH patients shown in the absence or presence of the IP antagonist, RO-11384525 (n=5). \*\*=*P*<0.01 compared to agonist.

IP agonist	Log EC <sub>50</sub> (n=5)	EC <sub>50</sub>	E <sub>max</sub>
MRE-269	-6.47 ± 0.43*	340 nM	25.1 ± 4.8%#*****
APD811	-6.60 ± 0.17*	252 nM	44.7 ± 3.2%****
Iloprost	-7.76 ± 0.27	17 nM	63.5 ± 9.6%***
Treprostinil	-6.20 ± 0.06**	550 nM	99.8 ± 3.1%

Table 1. Extrapolated EC<sub>50</sub> and E<sub>max</sub> values from mean fits where cAMP levels were normalized to maximal response-#=*P*<0.05 when compared to APD811; \*=*P*<0.05, \*\*\*=*P*<0.001 when compared to iloprost; +=*P*<0.05, +++=*P*<0.001 when compared to treprostinil

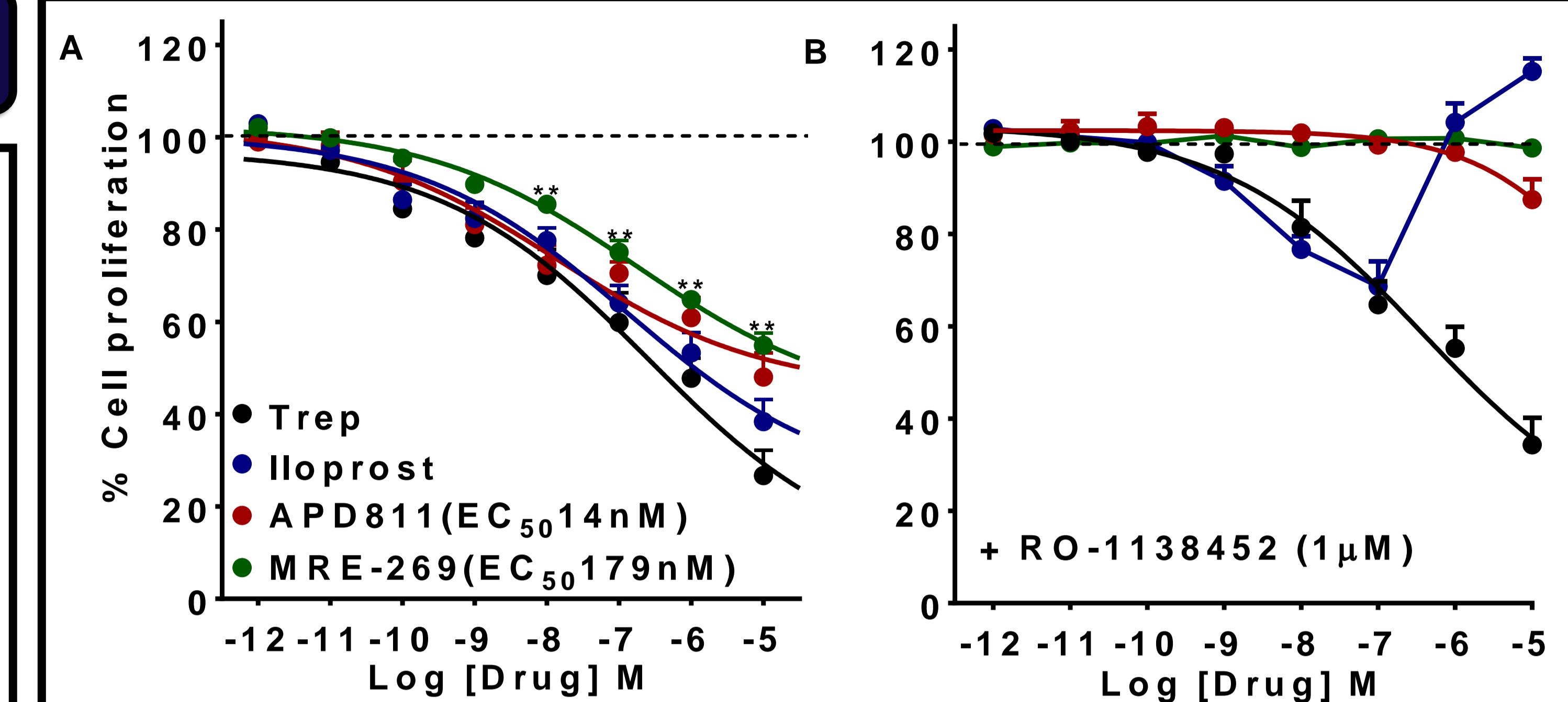


Figure 3. (A) Antiproliferative effect of IP agonists in PASMCs (n=5) where rank order of efficacy (*P*<0.05) was Treprostinil >iloprost=APD811>MRE-269. (B) Differential effect of RO-1138452 on agonist responses. \*\*=*P*<0.01 compared to treprostinil

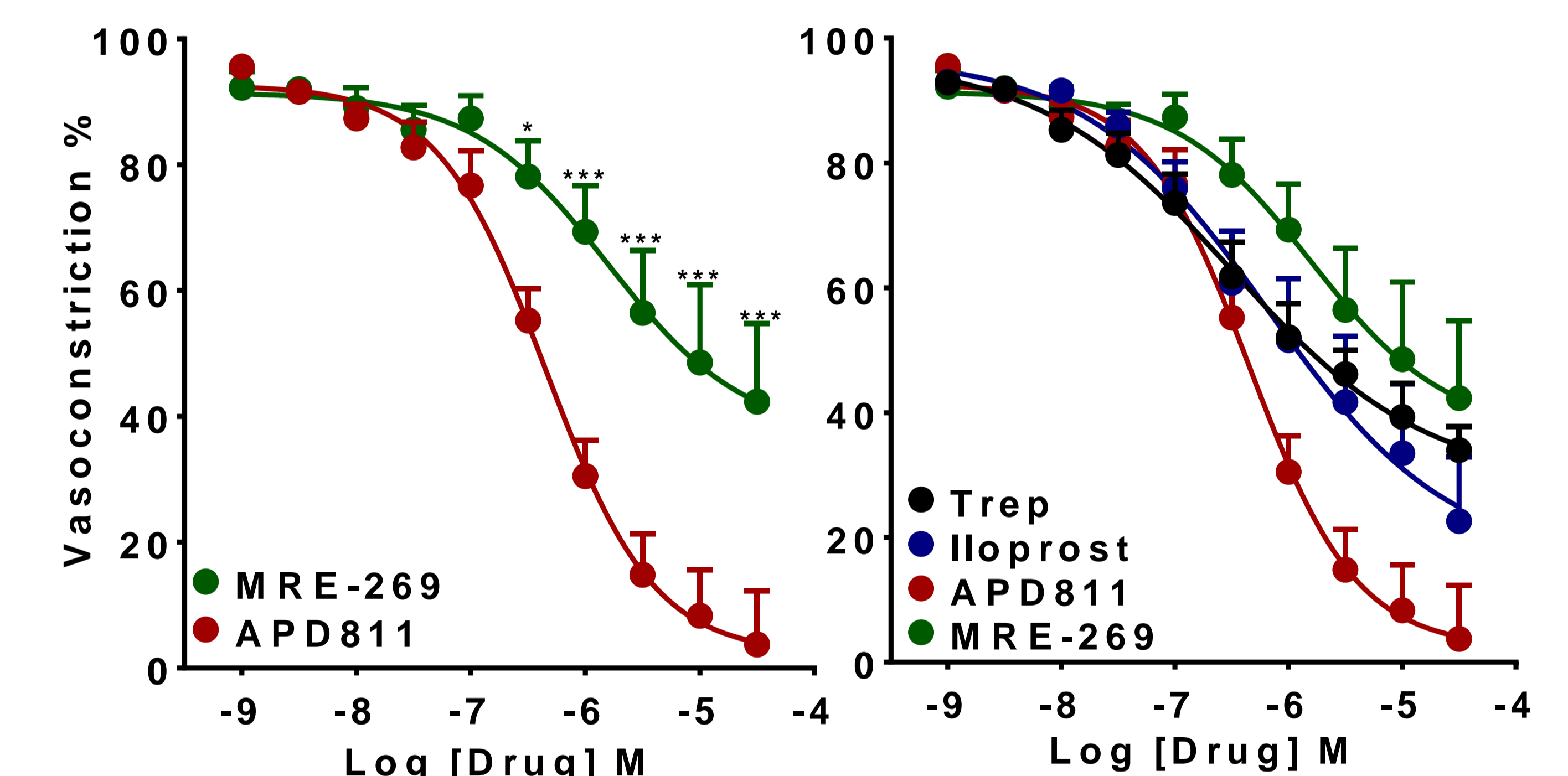


Figure 4. Mean concentration-response effects of prostacyclin mimetics mediating vasorelaxation of constricted PAs (9-12 vessels from 5-8 patients. Average relaxation to Ach in vessels was 18%.

## Conclusions

Ralinepag and selexipag metabolite behave as selective, but partial IP receptor agonists. Other mechanisms contribute to the functional effects of classical IP agonists. Ralinepag produced superior effects to selexipag metabolite in all functional assays and had a favorable vasodilator profile compared with iloprost and treprostinil.