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Title: GW870086: A potent anti-inflammatory glucocorticoid with a novel pharmacological profile

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Body: Inhaled glucocorticoids are highly effective therapies for respiratory diseases. Progress in characterising the complex molecular mechanisms that control glucocorticoid action raises the possibility that anti-inflammatory molecules with reduced side-effect liabilities can be identified. Here we describe the discovery of a novel glucocorticoid, GW 870086, with unique biological properties, and demonstrate the potential of gene expression profiling in the characterisation of its pharmacology. This molecule is under clinical evaluation as a novel respiratory agent. The pharmacological properties of GW870086 were assessed against fluticasone propionate (FP) using cellular and in vivo model systems, including extensive gene expression profiling. GW870086 repressed inflammatory cytokine release from primary lung epithelial cells with similar efficacy to FP, but in marked contrast to FP antagonised the effect of dexamethasone on MMTV driven reporter gene transactivation. GW870086 had a very significant effect on the expression of specific glucocorticoid regulated genes while having minimal impact on the expression of other known target genes, demonstrating unique regulation of gene transcription. In experimental in vivo models of irritant-induced contact dermatitis and ovalbumin-induced allergic inflammation models, GW870086 showed comparable anti-inflammatory efficacy to FP. GW870086 is a potent anti-inflammatory compound that has a unique ability to regulate a specific subset of genes that are normally effected by classical glucocorticoids. It has clear potential to be developed as a new topical steroid with a distinct safety profile to existing therapies.