

Are SABAs obsolete: the GINA model?

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YES!!

Faculty

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Disclosures

Consulting Fees: AstraZeneca, MedImmune, RIFM, Equillium, Theravance.

Fees for Non-CME/CE: AstraZeneca, Sanofi, Genentech.

Contracted Research: AstraZeneca, MedImmune, RIFM, Genentech.

Learning Objectives

- Review outcomes from SMART approaches in the management of asthma.
- Explain how β agonists induce bronchodilation.
- Define the non-genomic effects of steroids and their amplification of β agonist-induced bronchodilation in the treatment of asthma.

Bronchodilation

- **Does not require gene expression**
- **Predominantly an airway smooth muscle effect**
- **Globally, inhaled steroids and β agonists served as rescue therapy for 15 years.**

Clinical evidence

Asthma control end points, baseline and during SMART therapy

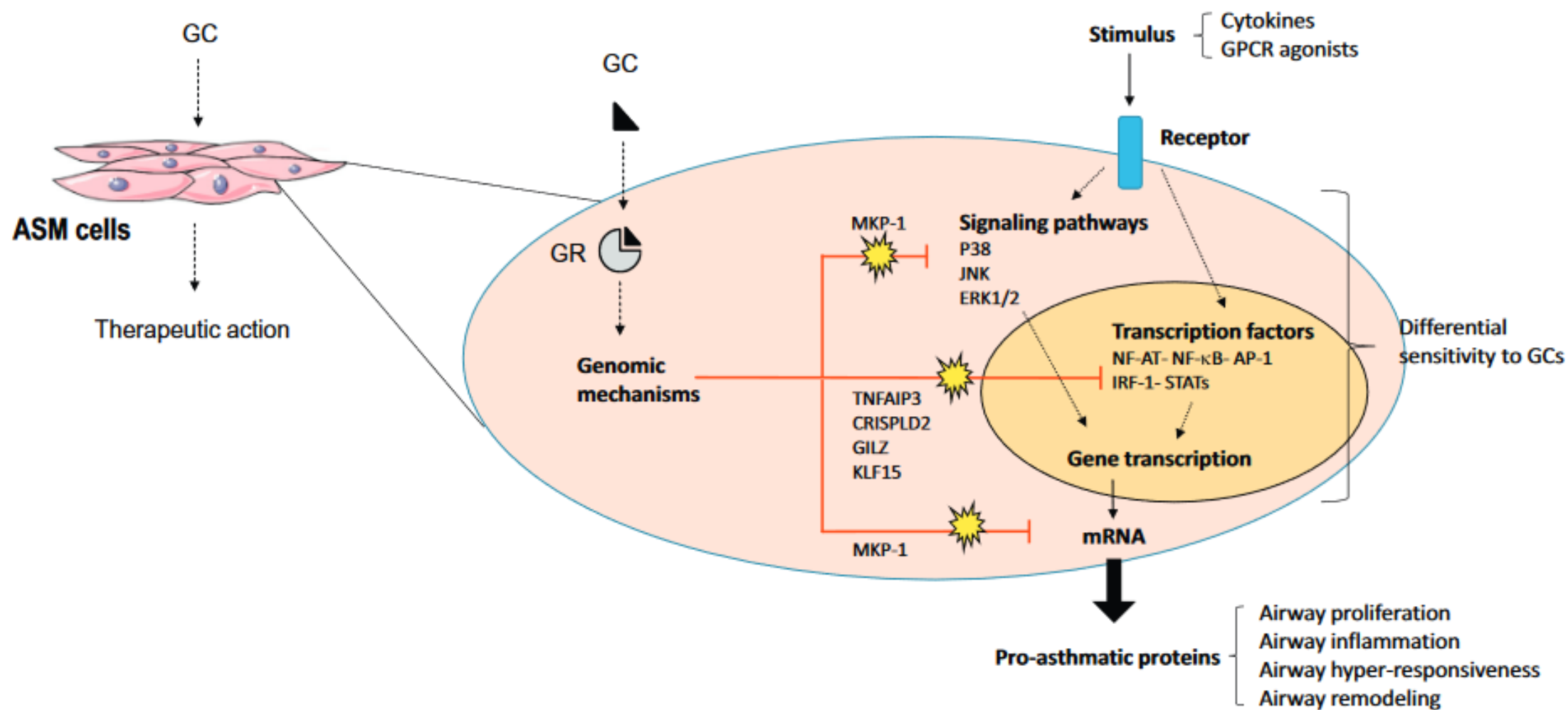
	Rabe <i>et al</i> ¹⁰	Scicchitano <i>et al</i> ¹¹	O'Byrne <i>et al</i> ¹²	Rabe <i>et al</i> ¹⁴	Vogelmeier <i>et al</i> ¹⁵	Kuna <i>et al</i> ²¹	Bousquet <i>et al</i> ¹⁹	Weighted averages
N (SMART arm)	354	947	925	1107	1067	1052	1151	
Study duration	6 months	12 months	12 months	12 months	12 months	6 months	6 months	N/A
Symptom-free days (%)	B: 29.6 T: 55.1	B: 9.8 T: 41.7	B: 23.1 T: 54	B: 9.2* T: 40.3*	NA	B: 9.3 T: 44.2	B: 10.7 T: 47.2	B: 13.2 T: 46.0
As-needed reliever use (inhalations/day)	B: 1.64 T: 1.04	B: 1.9 T: 0.90	B: 2.46 T: 1.01	B: 1.8 T: 1.02	B: 2.6 T: 0.59†	B: 2.29 T: 1.02	B: 2.23 T: 0.95	B: 2.18 T: 0.92
Reliever-free days (%)	B: 24.3 T: 55.3	B: 29.3 T: 59.8	B: 8.2 T: 55	B: N/A T: 52	NA	B: 8.9 T: 56	B: 10.3 T: 58.2	B: 14.7 T: 56.1
Nights with awakenings (%)	B: 13.3 T: 6.5	B: 22.6 T: 9.4	B: 21.8 T: 9.0	B: 31.1 T: 14.1	NA	B: 33.7 T: 14.1	B: 32.1 T: 12.0	B: 27.7 T: 11.5
Severe exacerbations (events/patient/year)	0.08	0.23	0.19	0.19	0.24	0.24	0.25	0.22

*24-hour period.

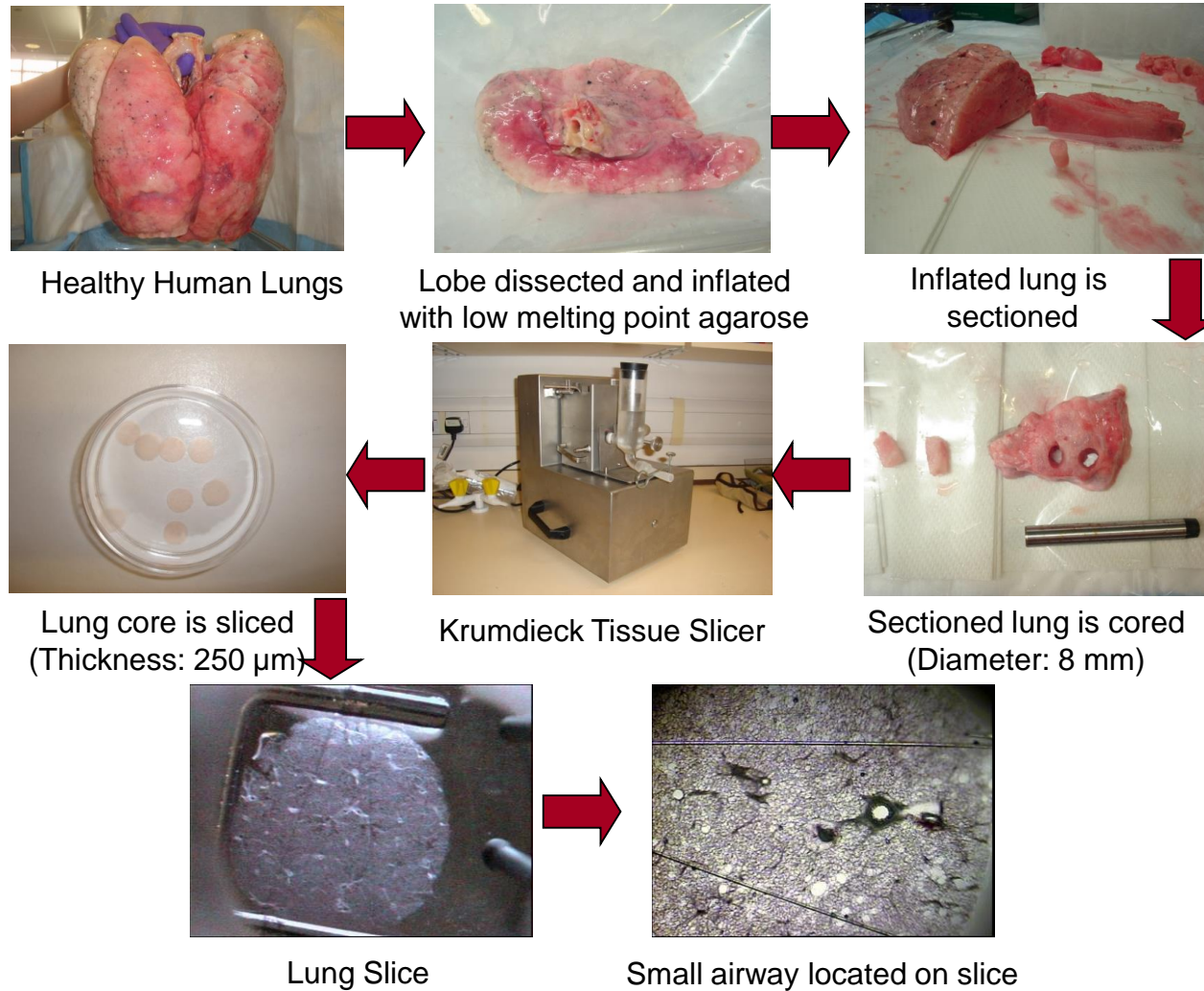
†For weeks 0–4 (during which morning and evening budesonide/formoterol doses were unchanged at two inhalations of 200/6).

B, baseline; T, treatment; NA, not available; N/A, not applicable; SMART, single maintenance and reliever therapy.

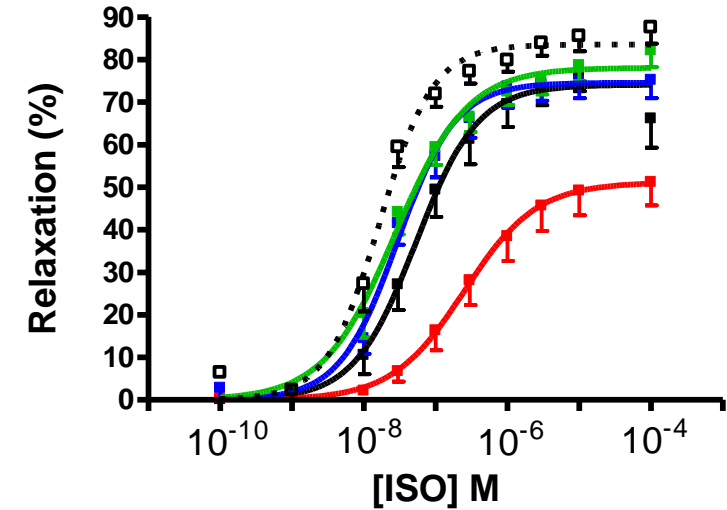
Genomic Effects of Glucocorticoids on Structural Cells



Preparation of Human Precision-Cut Lung Slices (PCLS)



Steroids restores β -AR responsiveness to isoproterenol.



- Control
- Albuterol (12 hrs, 0.1 μM)
- Dex (1.0 μM) + Albuterol (0.1 μM)
- Dex (1.0 μM)
- FP (0.1 μM) + Albuterol (0.1 μM)

EC₅₀ Values (μM):

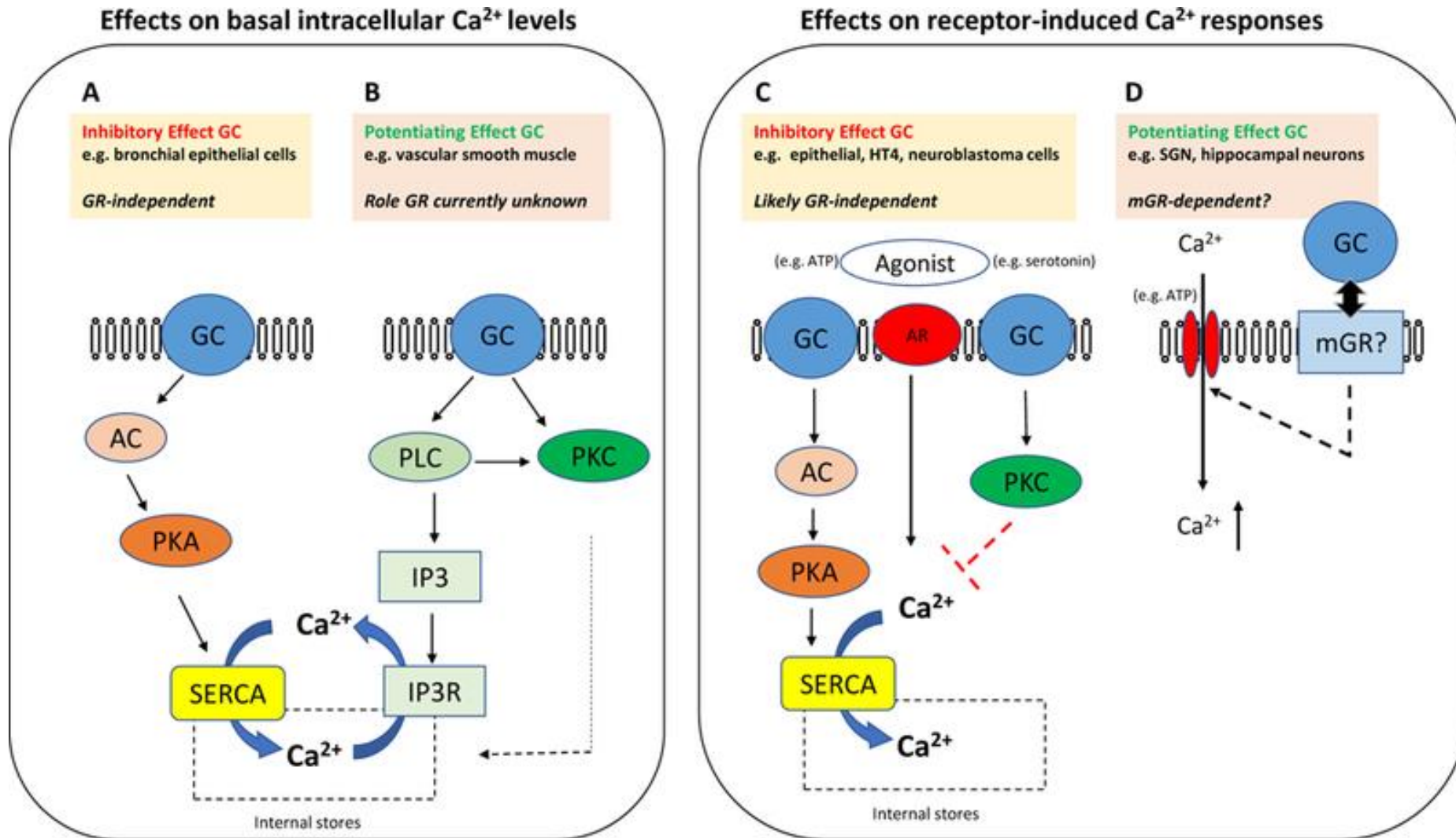
Control	Albuterol	Dex + Alb	FP + Alb	Dex
0.053	0.25	0.030	0.028	0.017

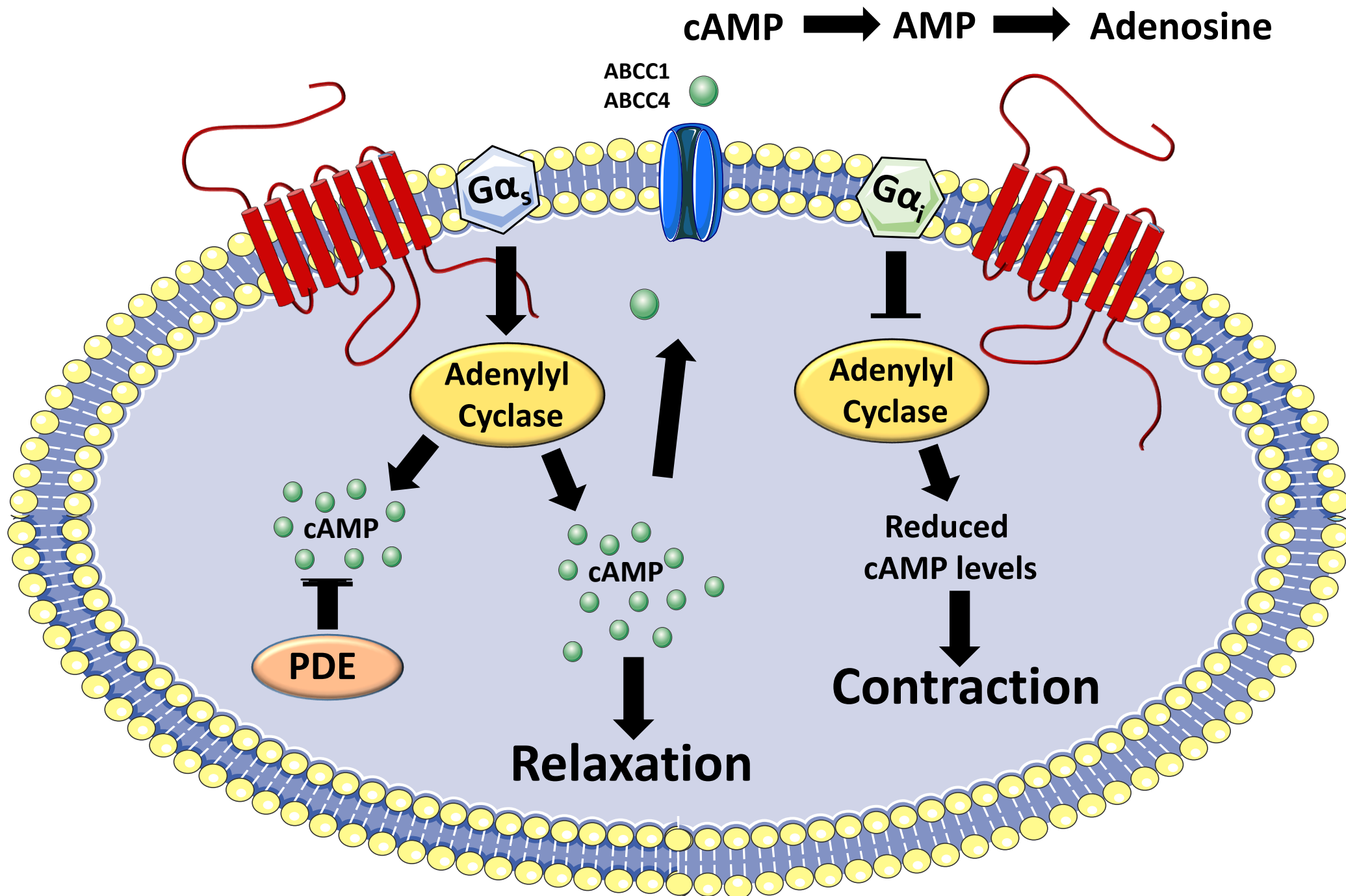
Cooper PR, Panettieri RA Jr. Steroids completely reverse albuterol-induced beta(2)-adrenergic receptor tolerance in human small airways. *J Allergy Clin Immunol.* 2008 Oct;122(4):734-740.

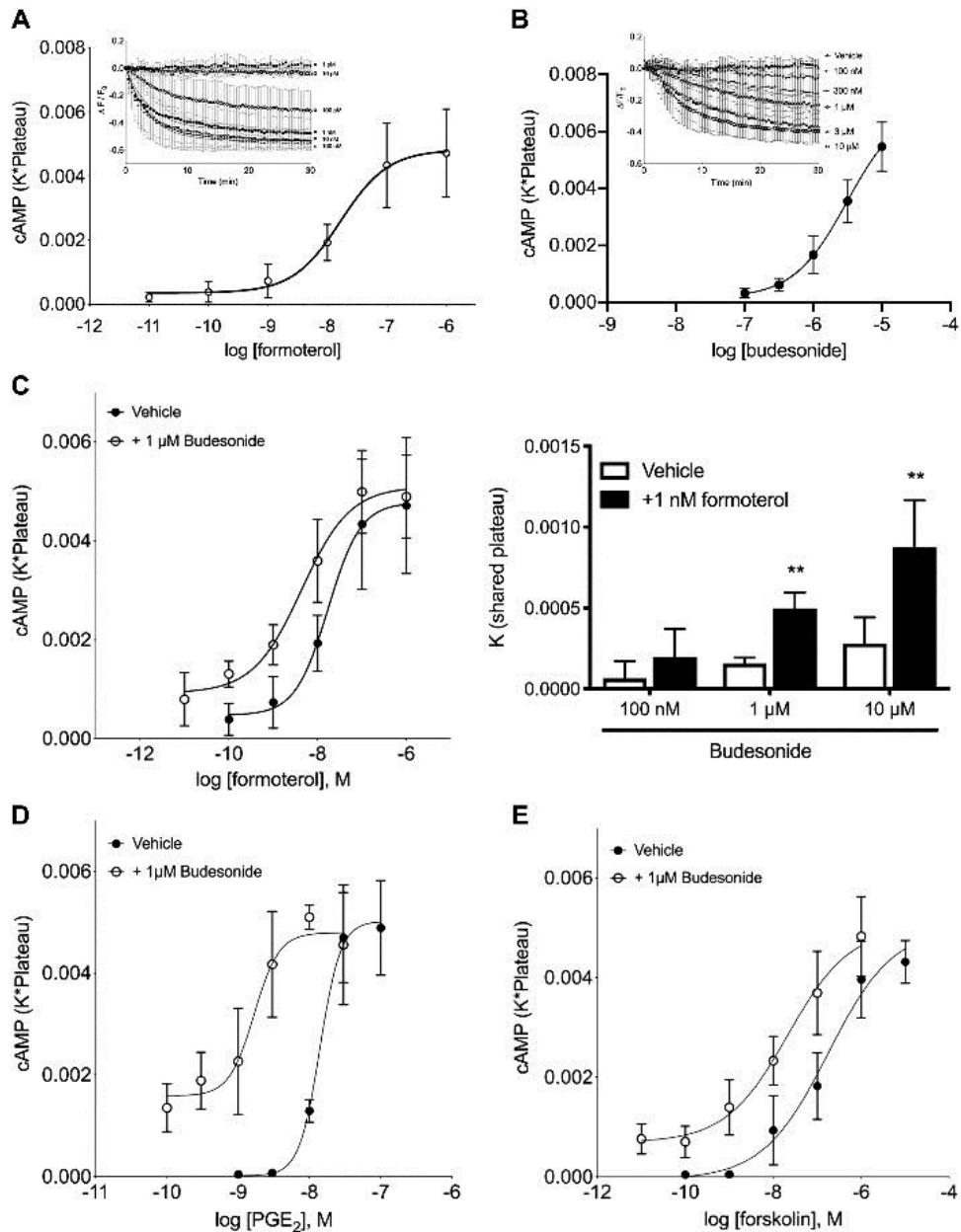
Distinguishing Genomic and Non-genomic Effects of Glucocorticoids

GC EFFECTS	ACUTE (simultaneous or within 30 minutes)	Chronic (delayed)
Genomic Effects	-	-
Inhibitory effects of CHX or Actinomycin D	-	+
GR involvement	- or +	+
Inhibitory effects of RU486	- or +	+
Type of GR involved	None, membrane GR or cytosolic GR	Cytosolic GR
GR-independent mechanisms	GC interaction with membrane	None

Glucocorticoids and GR Effects on Structural Cells

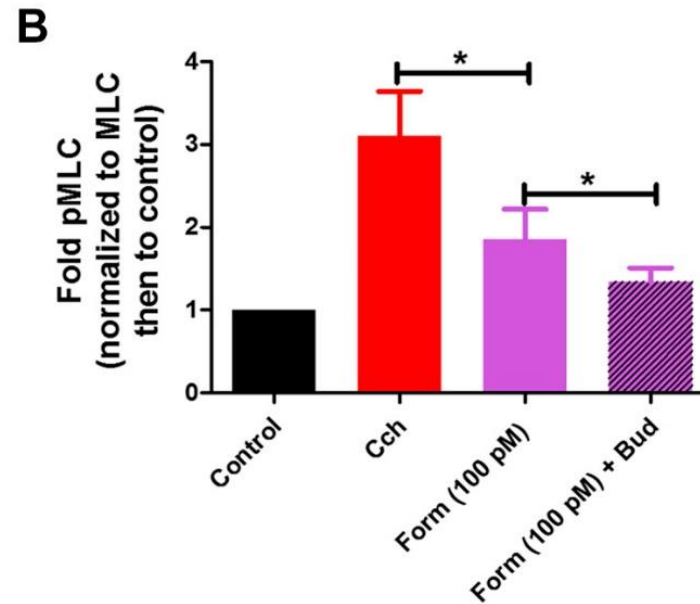
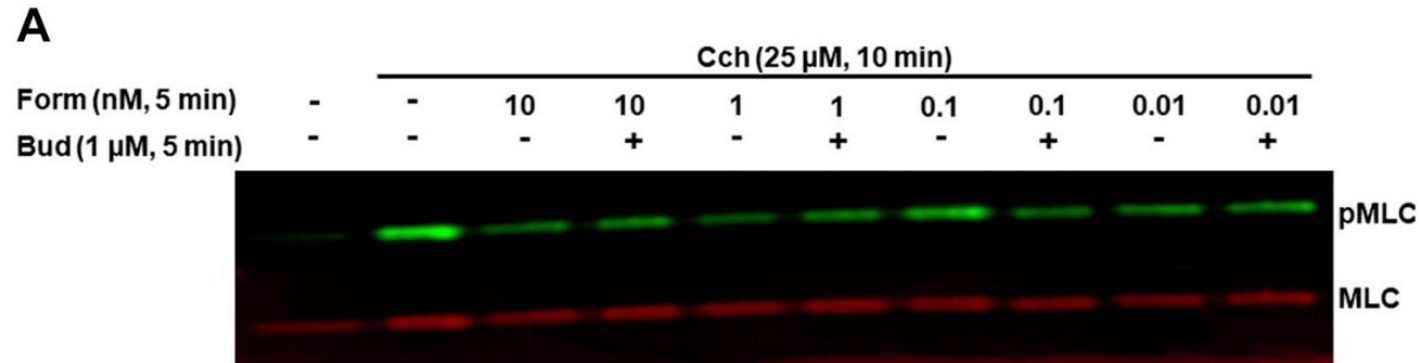




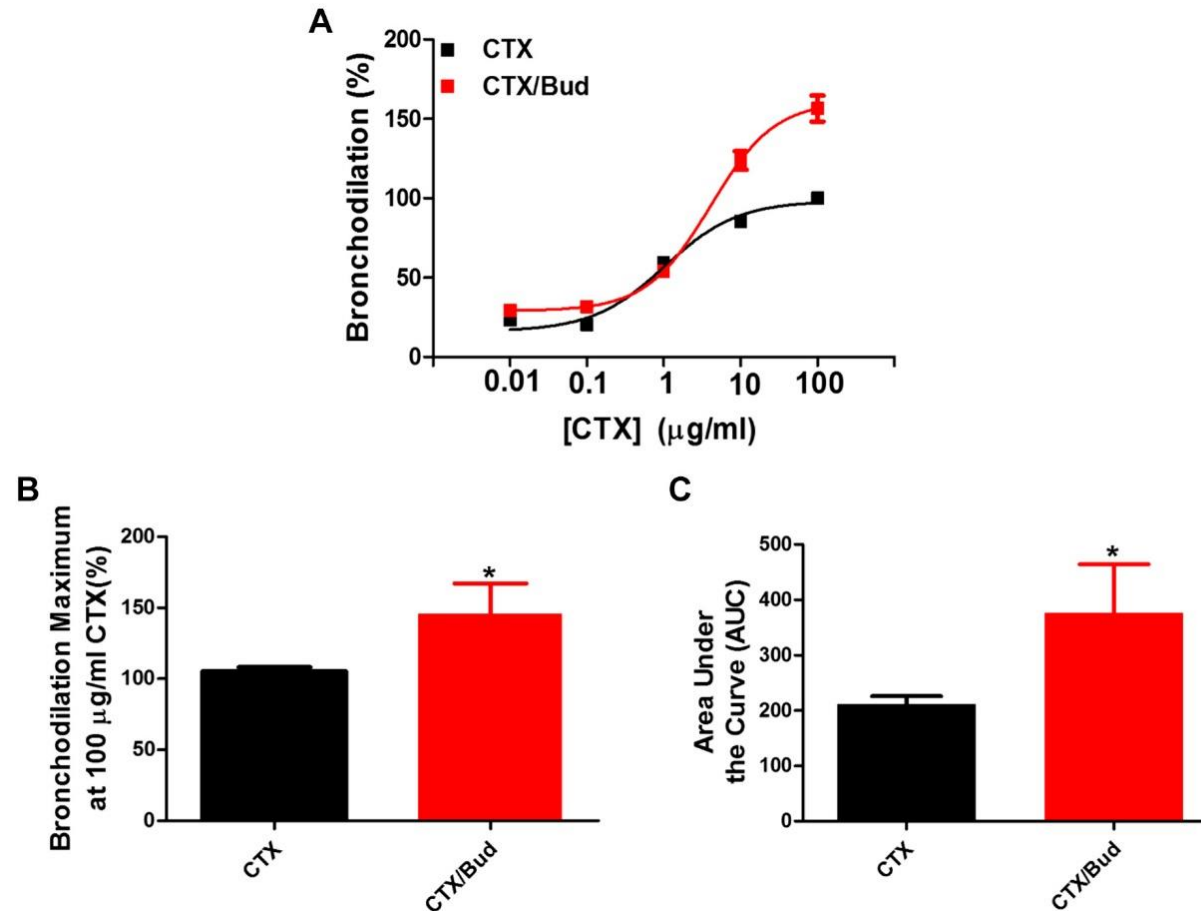


Budesonide alone increases cAMP levels and amplifies that induced by formoterol, PGE2 or forskolin

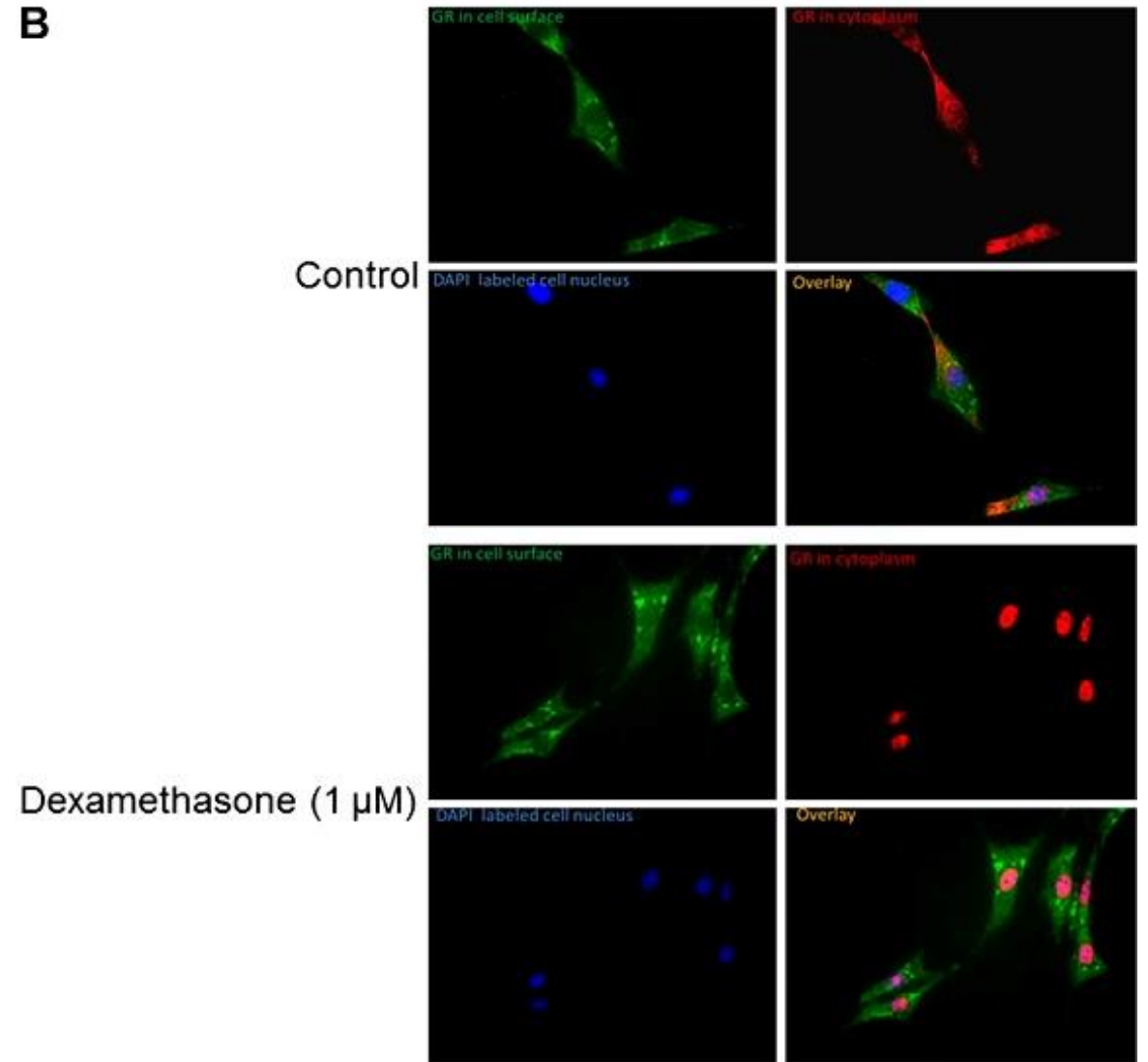
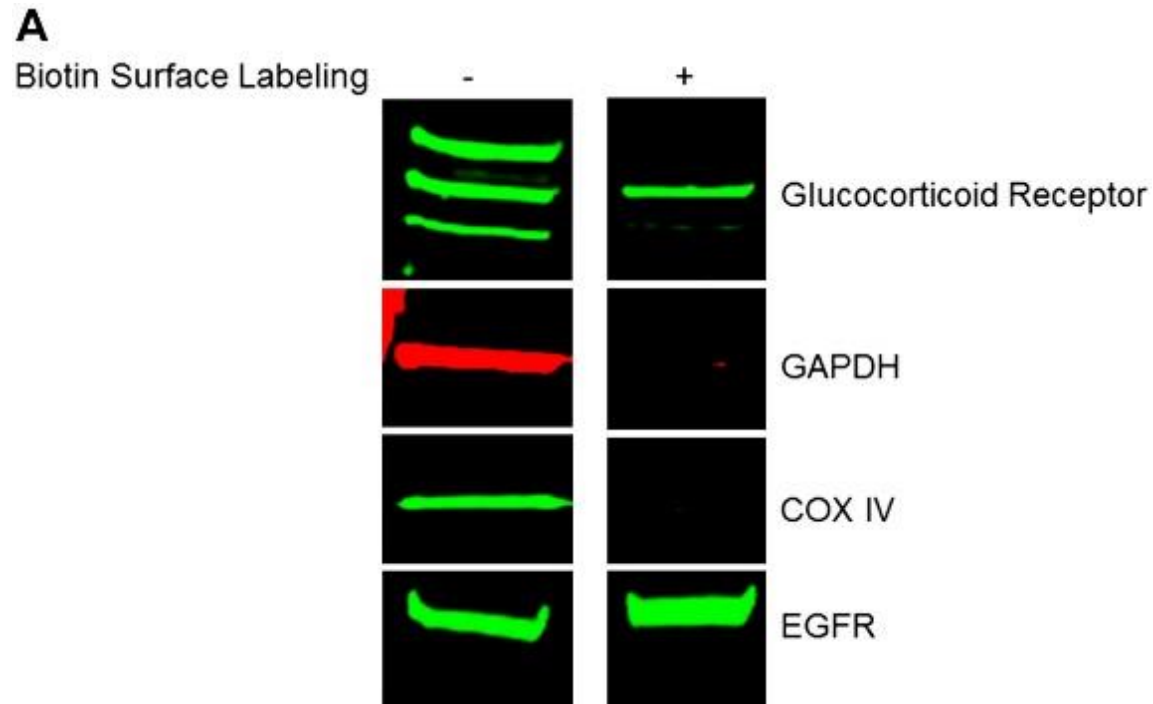
Budesonide Augments Formoterol-induced Inhibition of Carbachol-induced pMLC

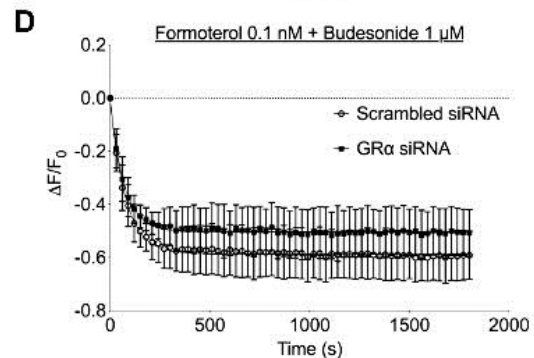
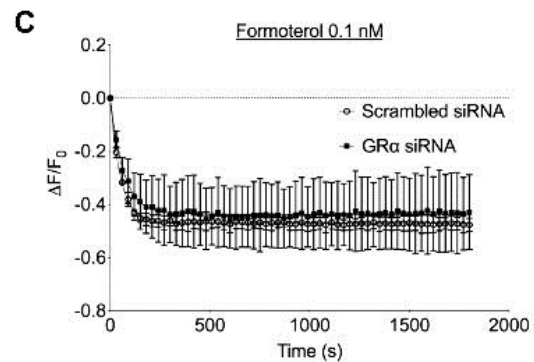
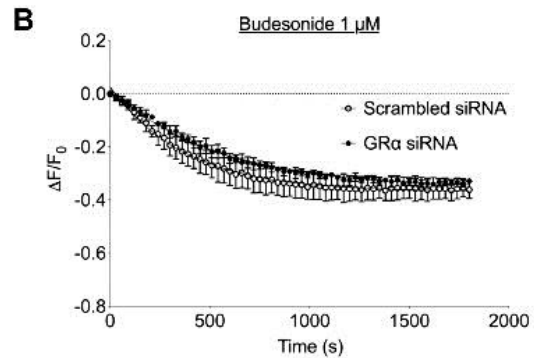
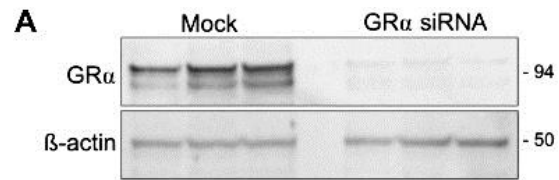


Budesonide Significantly Augments Cholera Toxin-Induced Bronchodilation of Human Small Airways



HASM Cells Express Membrane-Associated GR





Knockdown of glucocorticoid receptor- α (GR α) had little effect on budesonide or budesonide + formoterol-induced cAMP production in human airway smooth muscle (HASM).

Summary

- **The presence of steroids prevents β 2AR desensitization in human small airways.**
- **The combination of budesonide and a β agonist enhances β agonist-induced bronchodilation.**
- **Budesonide primes human airway smooth muscle to generate more cAMP.**
- **Budesonide effects on β agonist-induced bronchodilation occurs acutely and likely mediated in a non-genomic manner.**

Not a Black Box, but a Green Box!!

Concerning bronchodilation, there is little reason to use a β agonist alone since β agonists alone are inferior bronchodilators compared with that of a budesonide/ β agonist combination.