

# EPIGENETIC MODIFICATION FOR THE FUTURE TREATMENT OF INFLAMMATORY DISEASE

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Imperial College



Royal Brompton Hospital

## THERAPEUTIC POTENTIAL OF EPIGENETICS

**EPIGENETICS:** non genetic changes in chromatin structure resulting in changes in gene expression

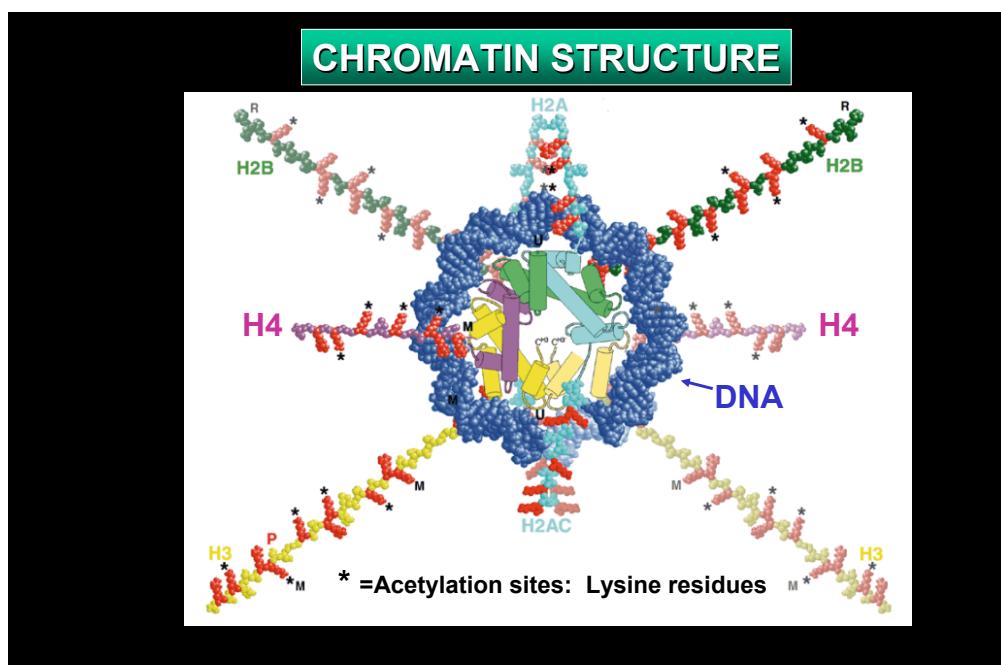
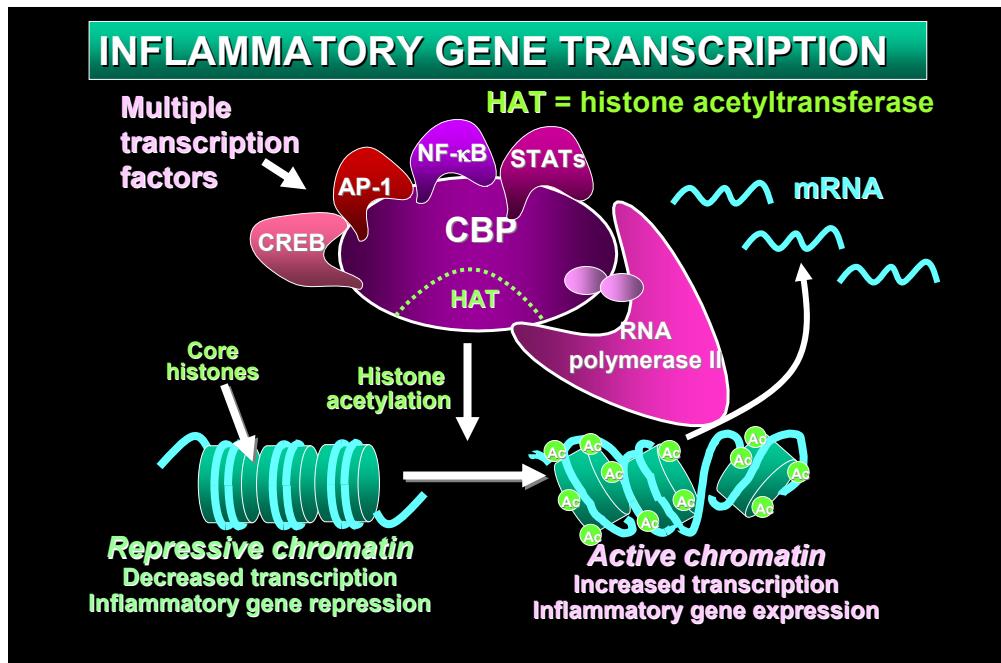
- DNA methylation- long-term changes, developmental
- Histone modification

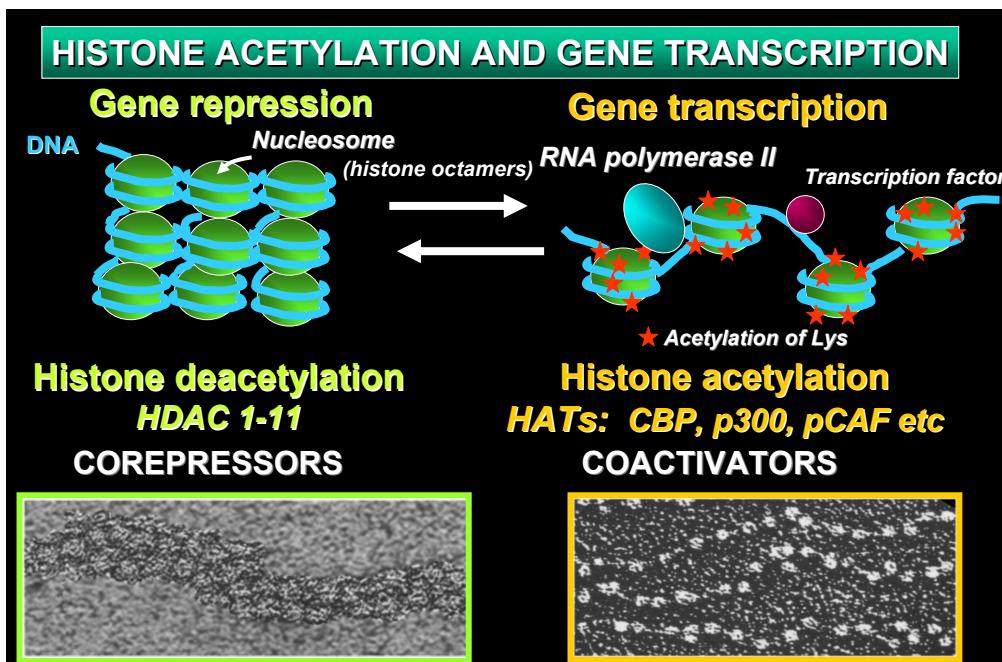
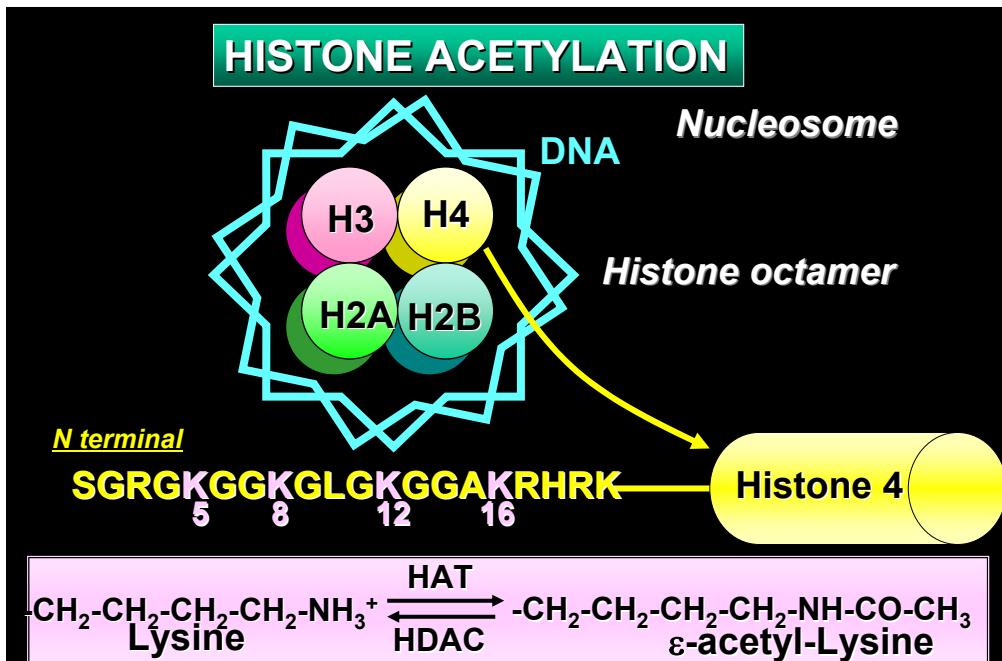
### **DNA methylation**

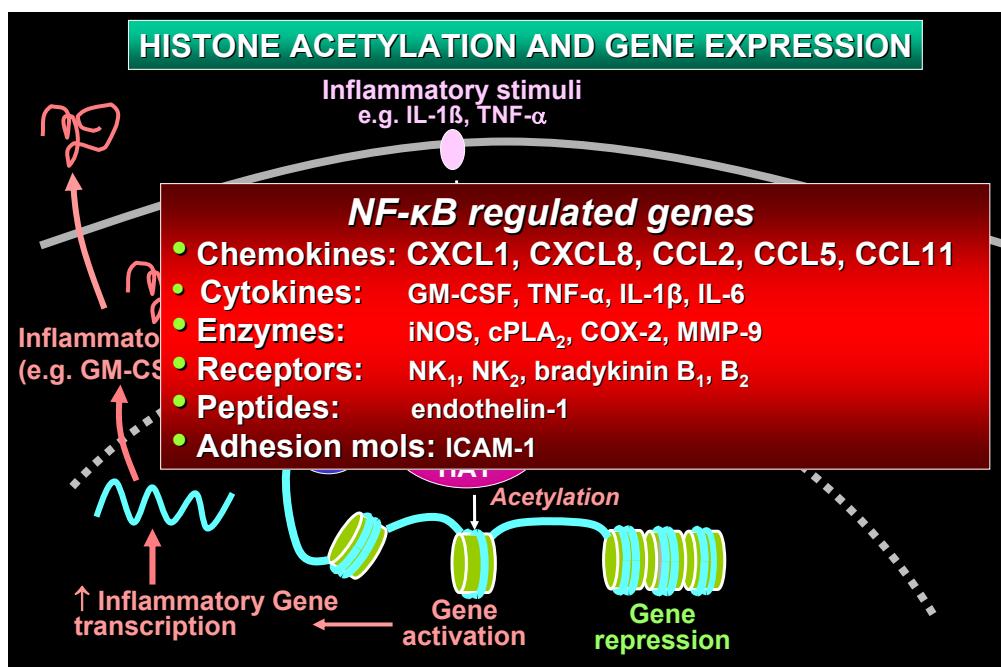
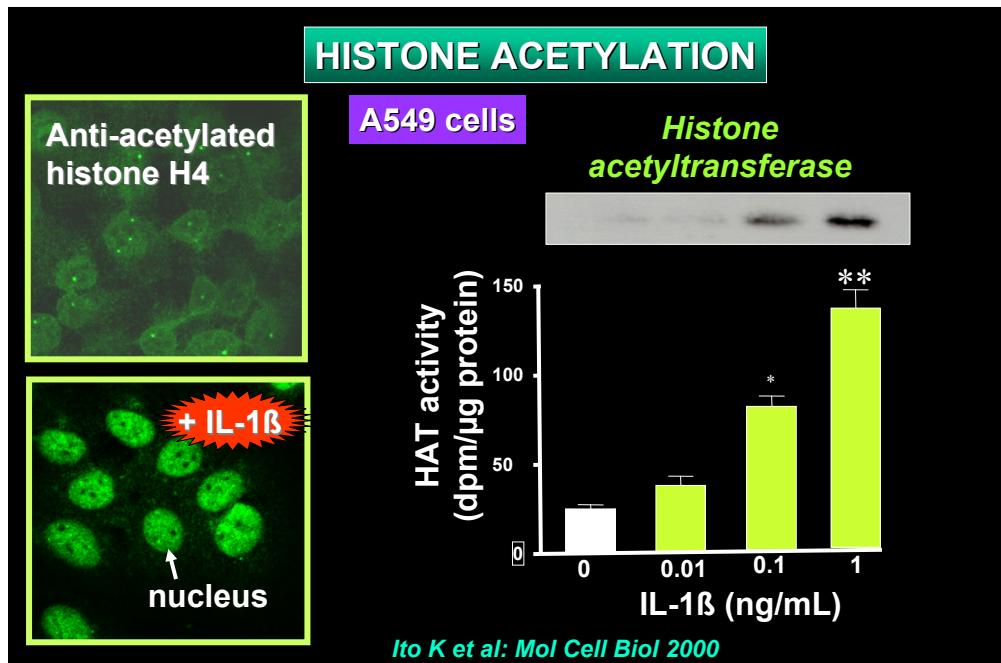
- DNA methyltransferase inhibitors (e.g. azacytidine): reverse silencing of good genes
- Stimulate methylation: silence bad genes
- Applicable to lung cancer, inflammation?
- Problems of specificity and targeting

### **Histone modification**

- Involved in cancer, fibrosis, inflammation
- Small molecule modifiers now identified (including existing therapies)



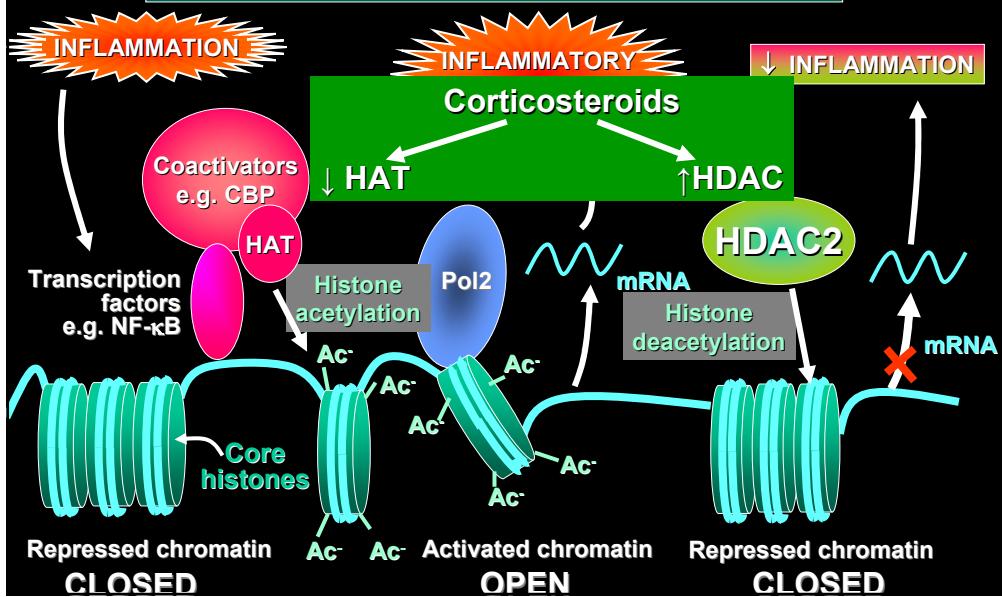


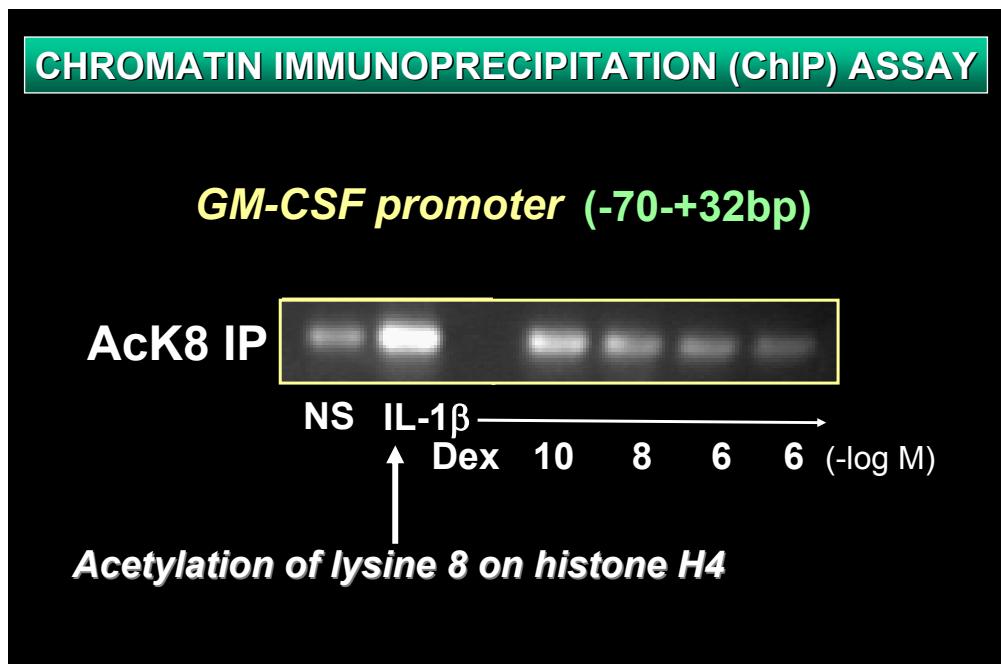
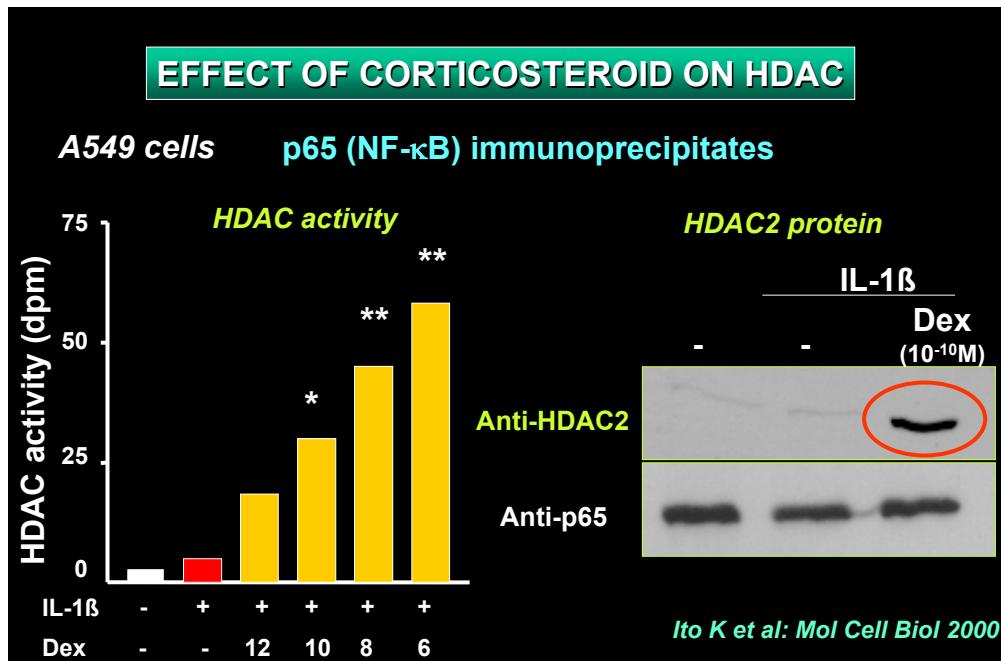


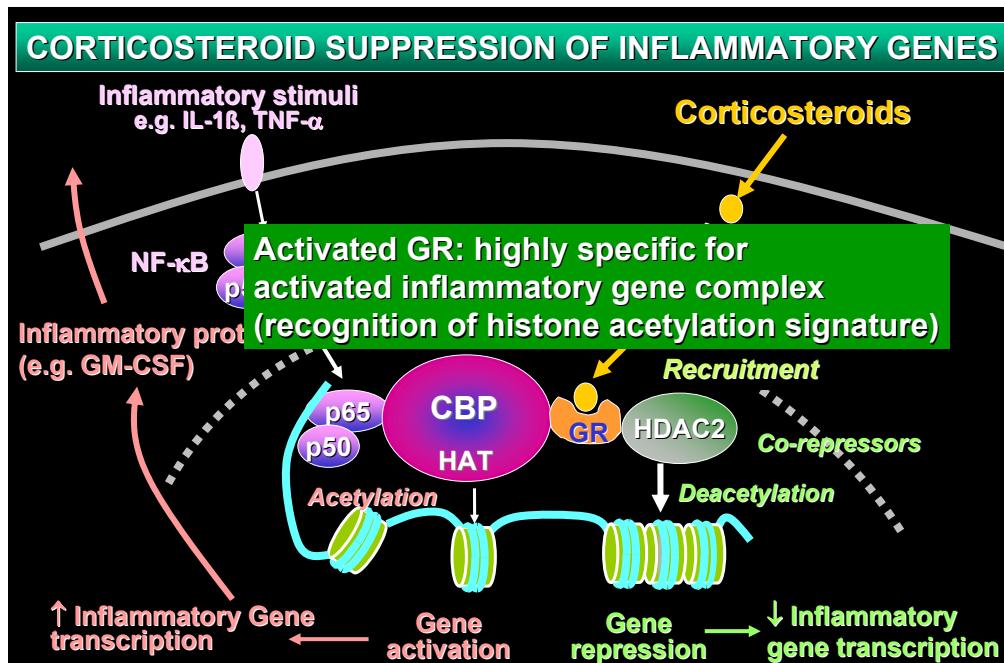
## ACTIVATION OF INFLAMMATORY GENES

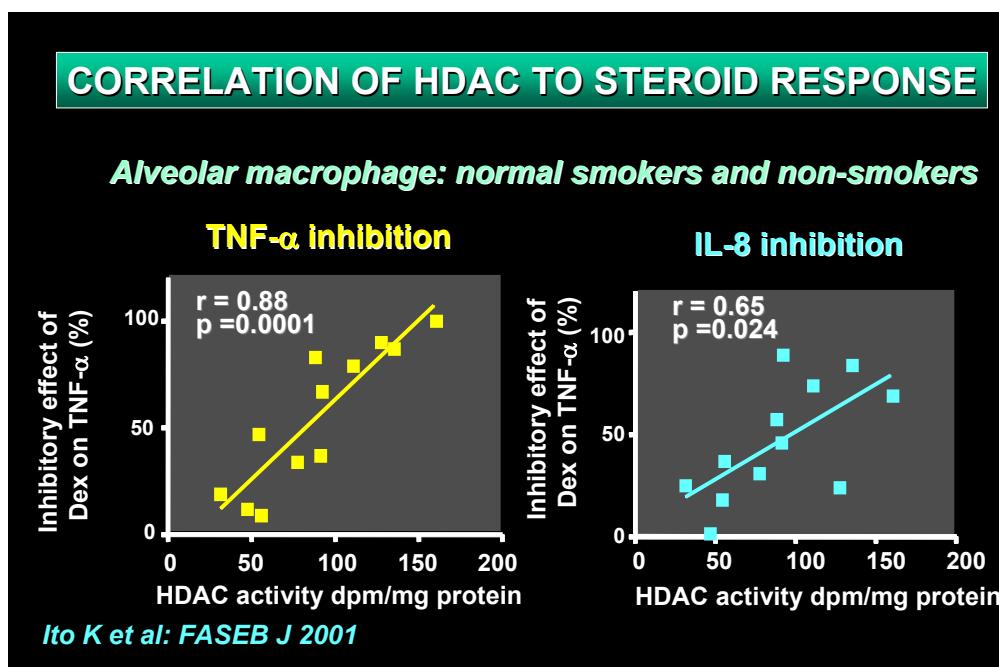
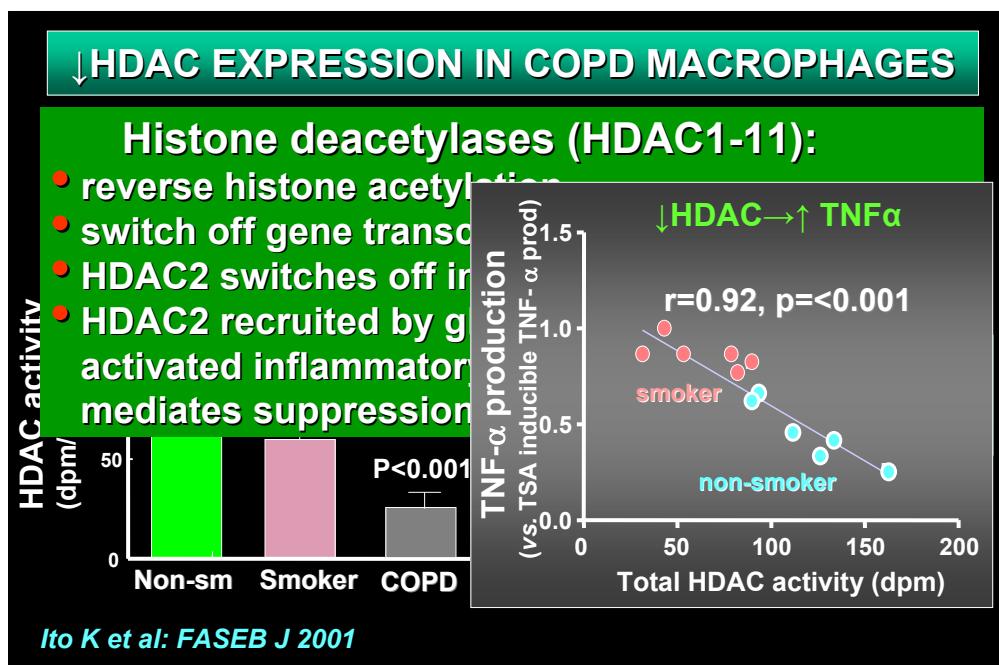


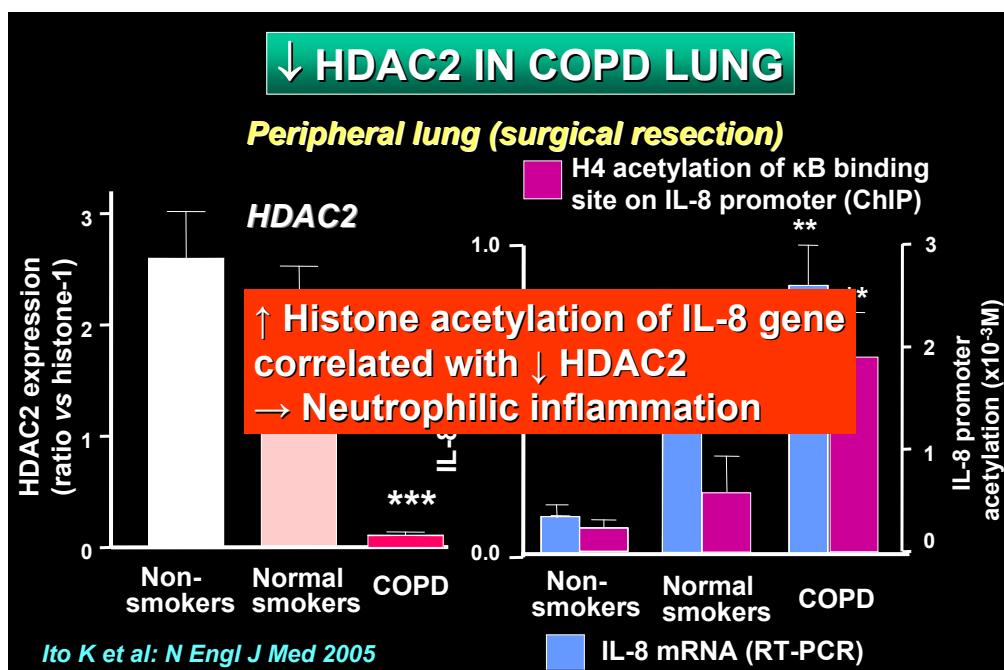
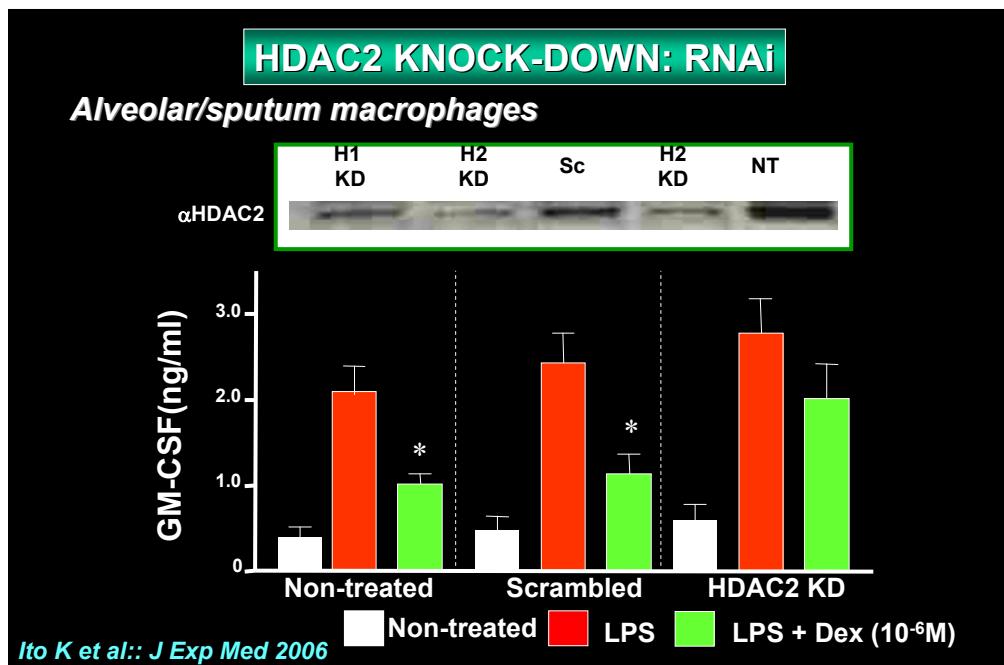
## INFLAMMATORY GENE REGULATION

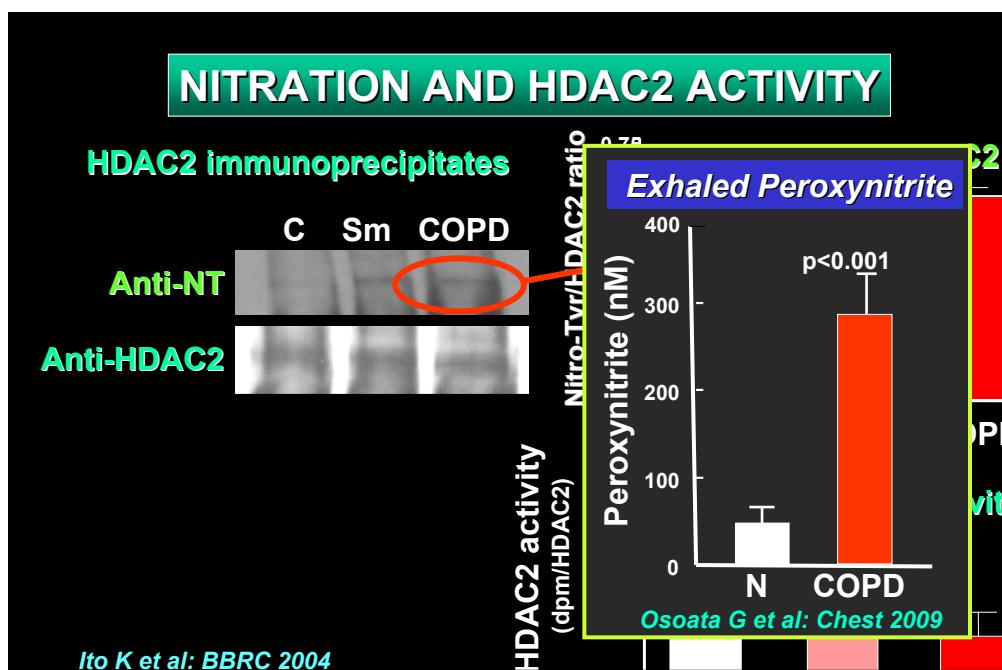
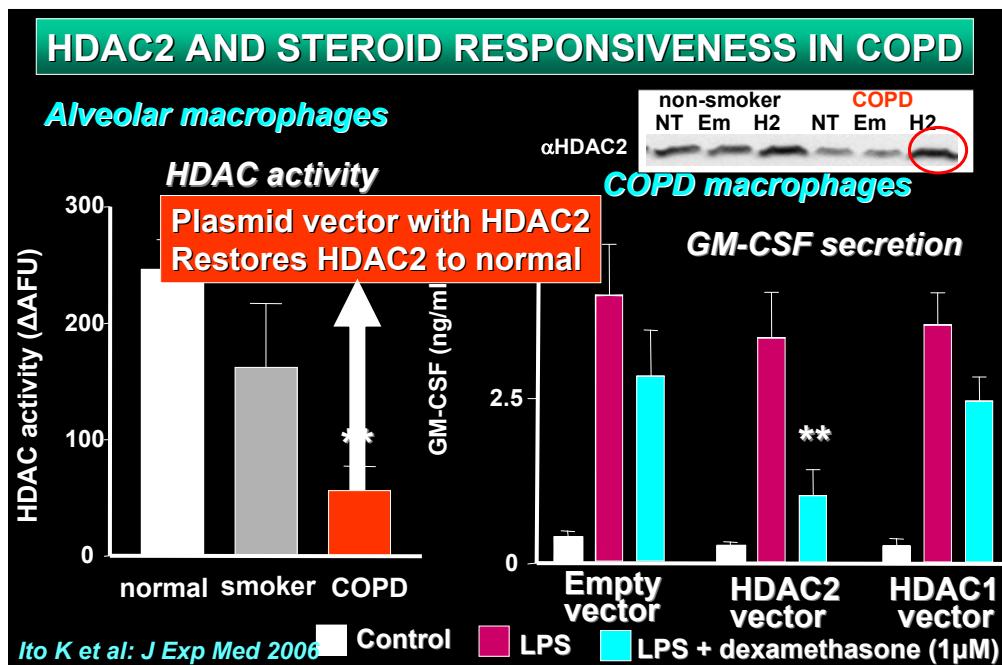


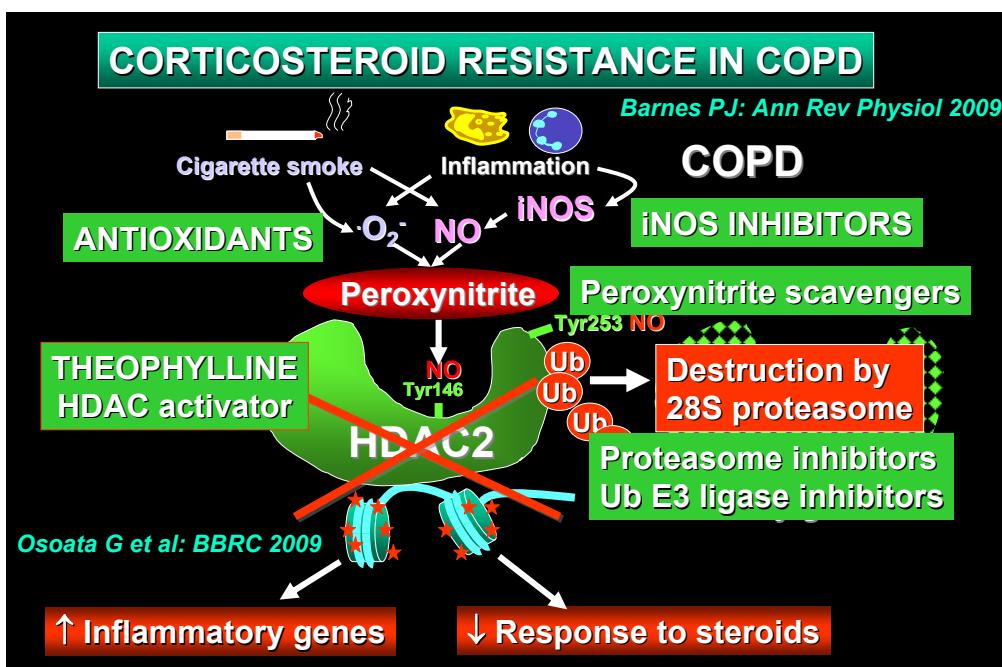
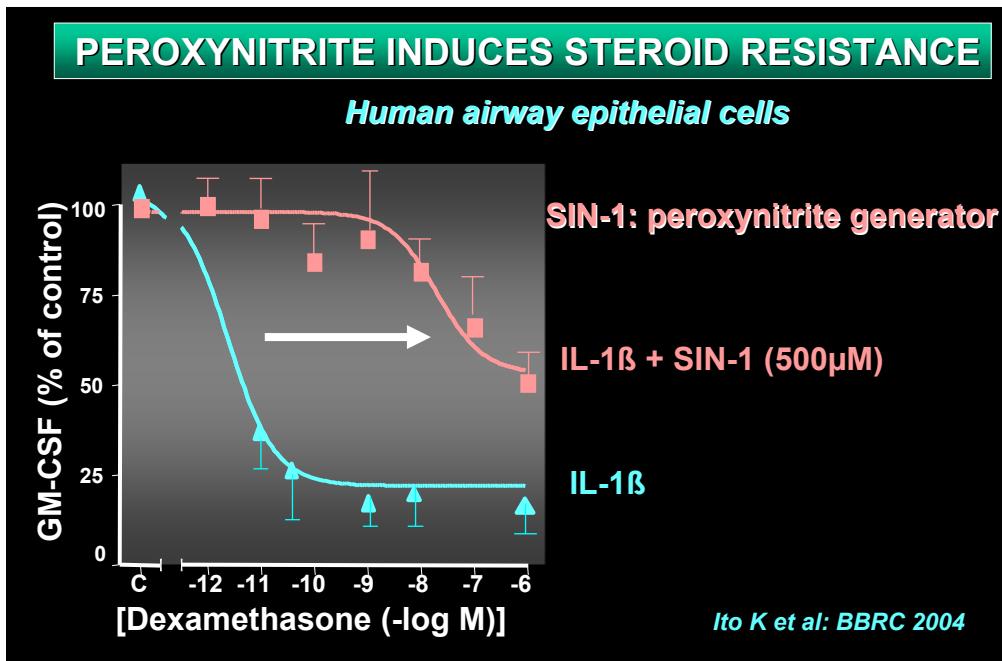


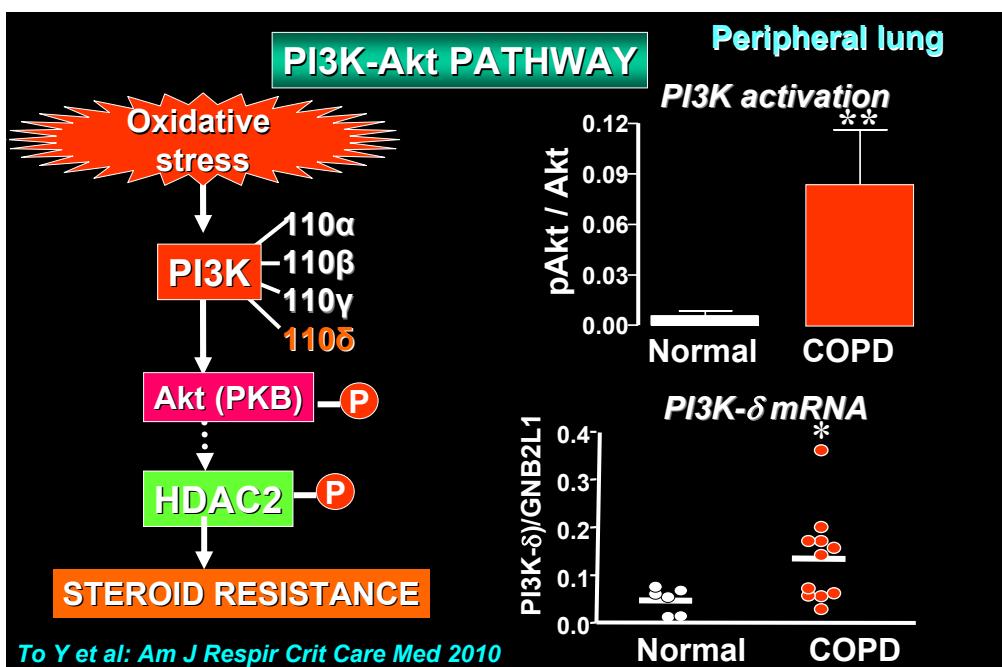
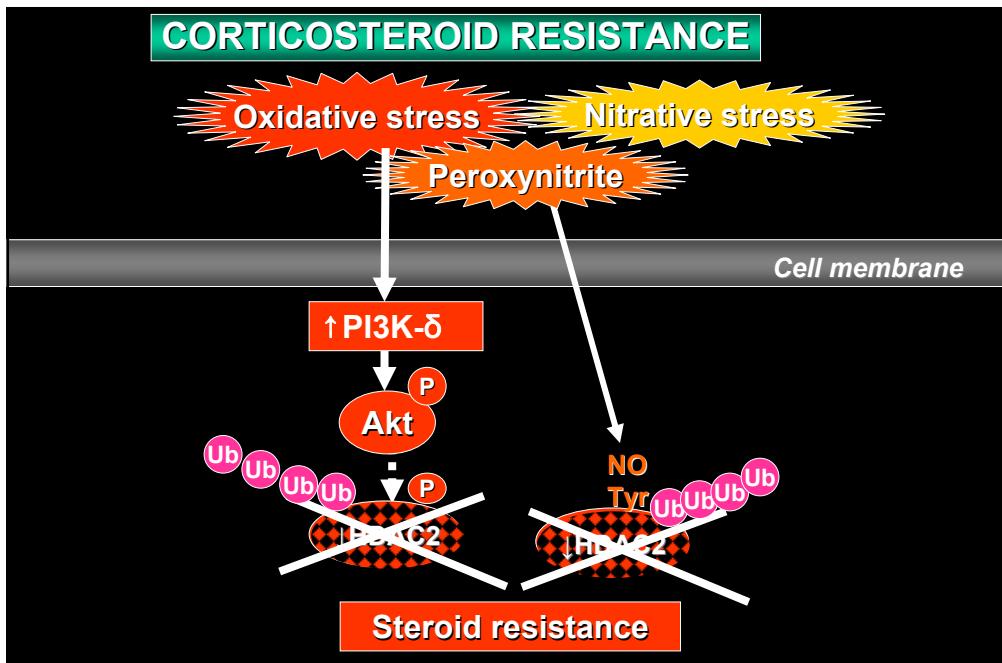


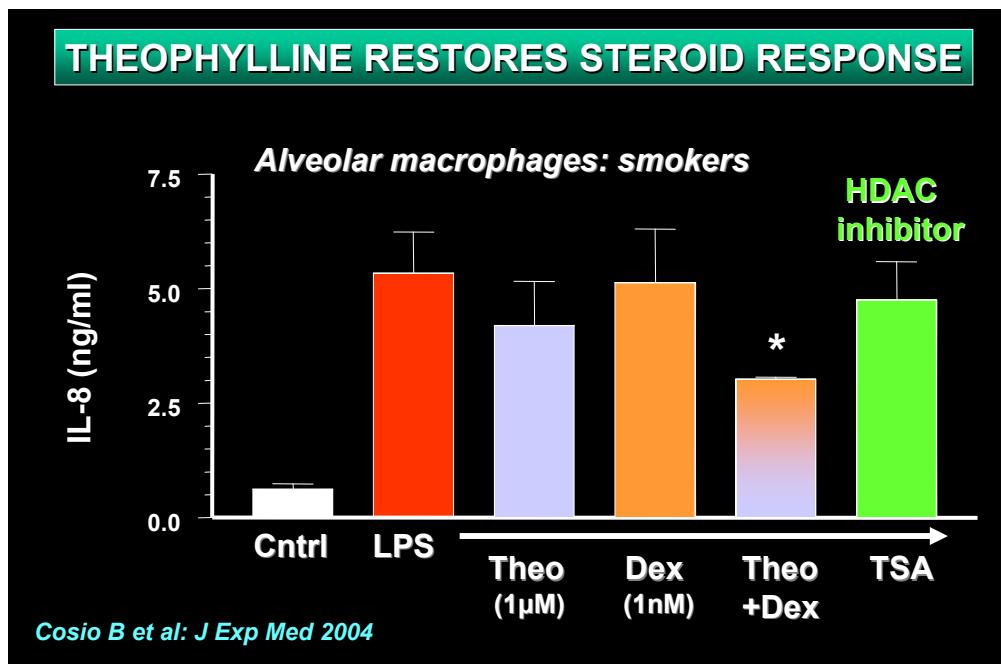
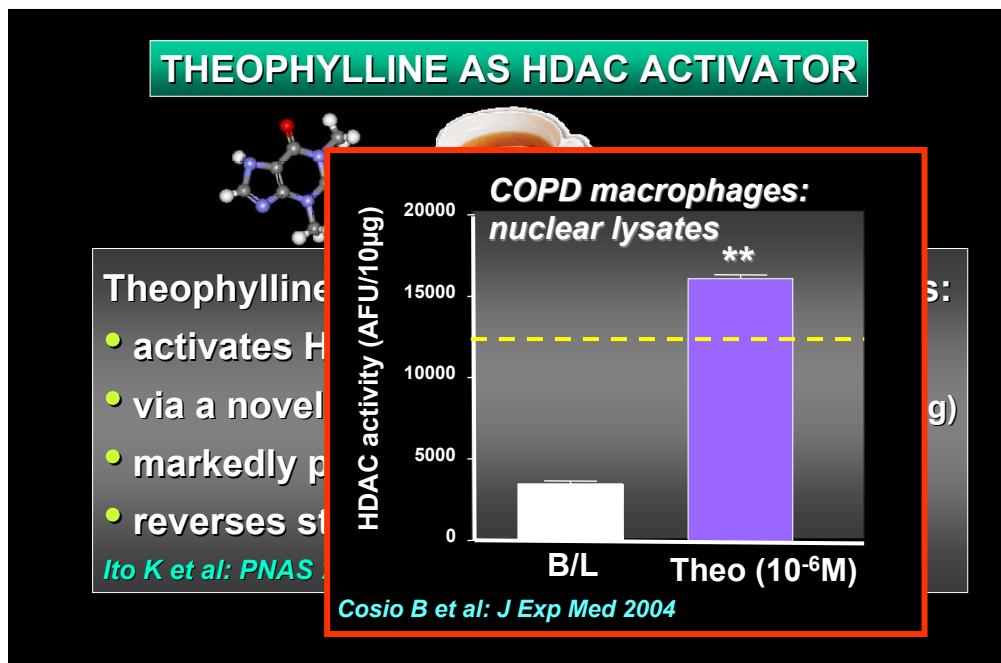


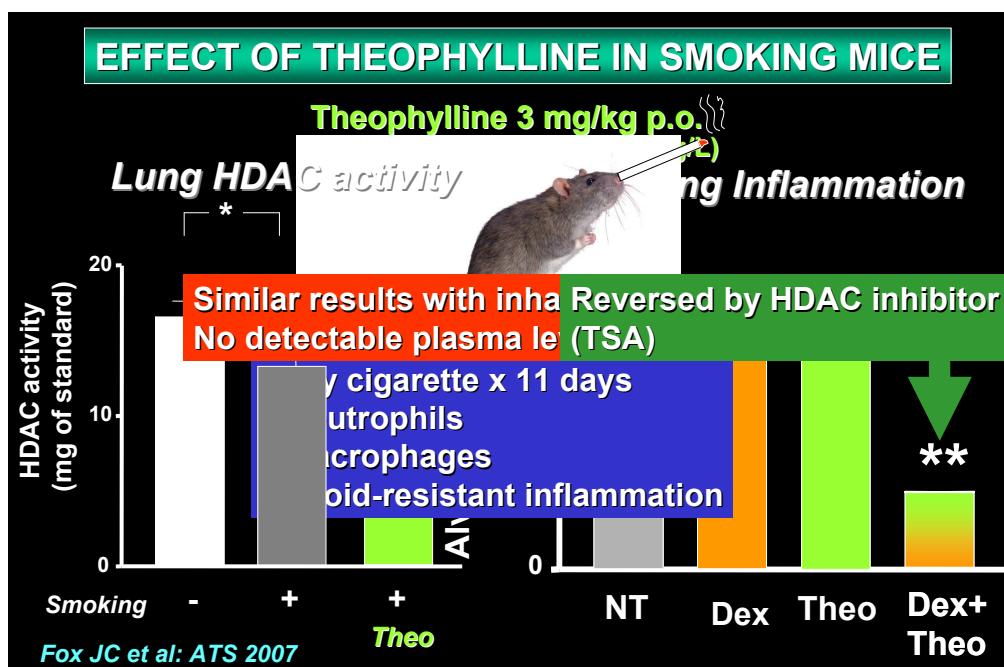
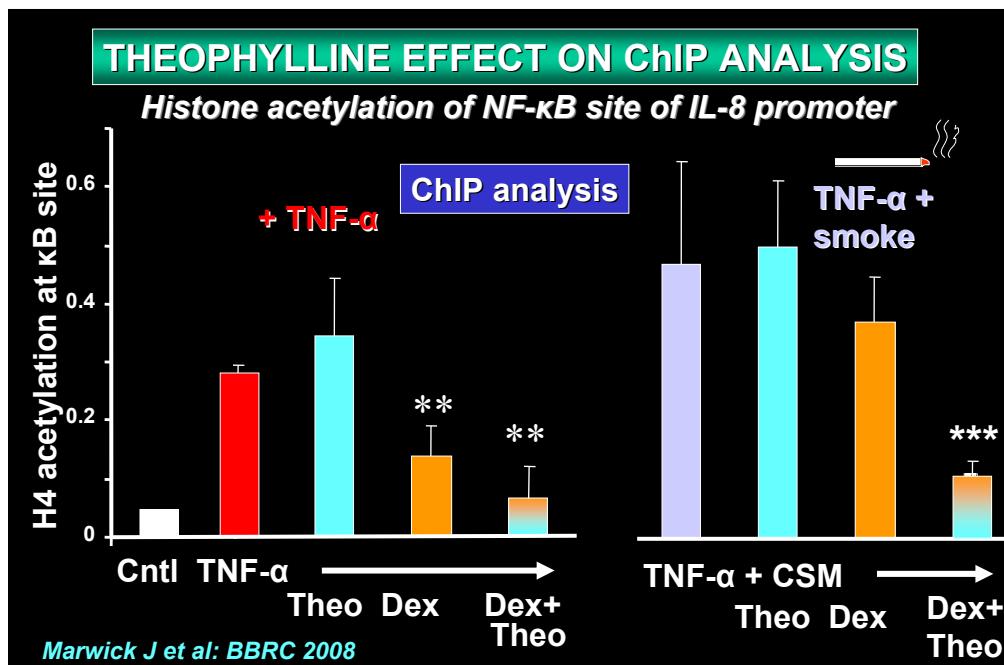


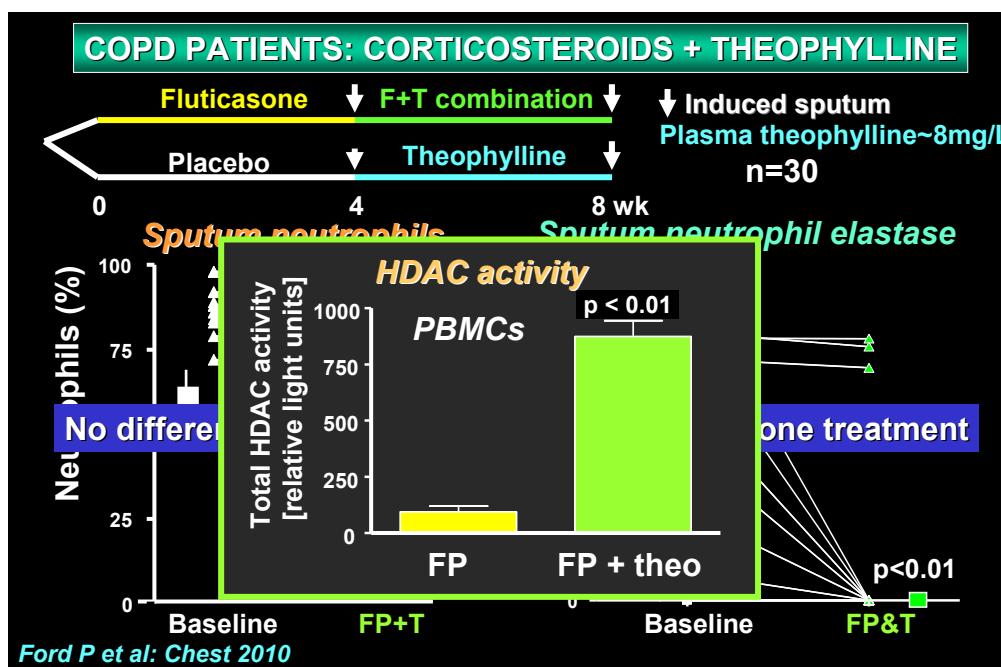
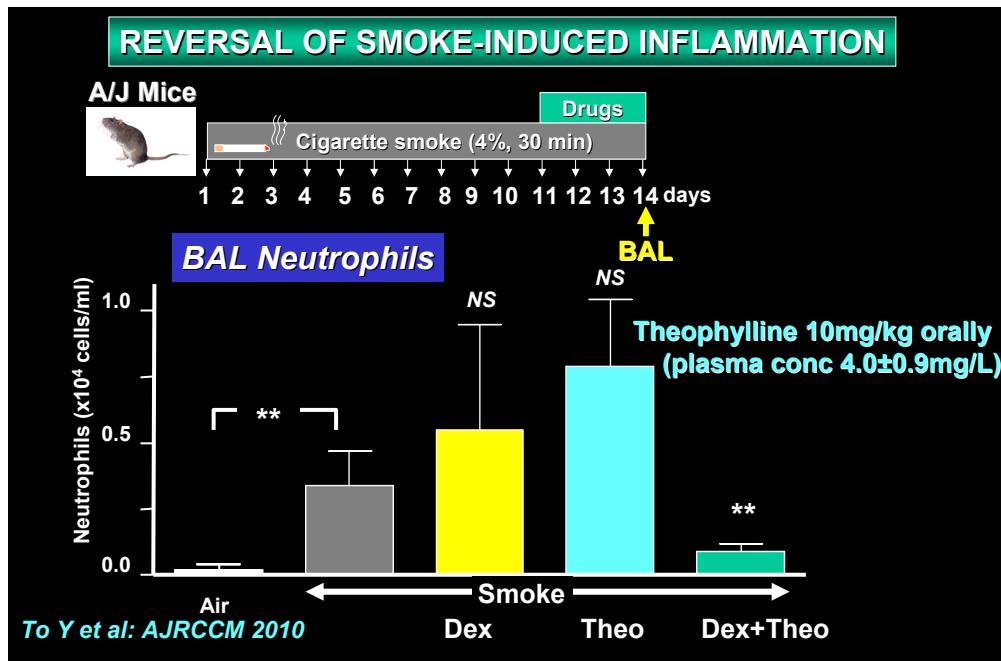


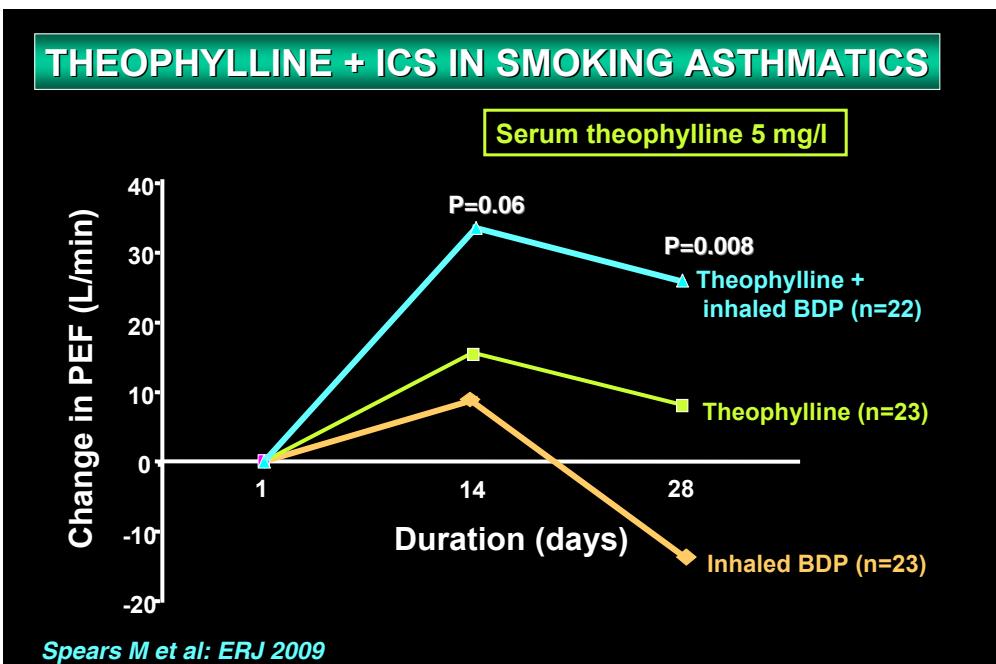
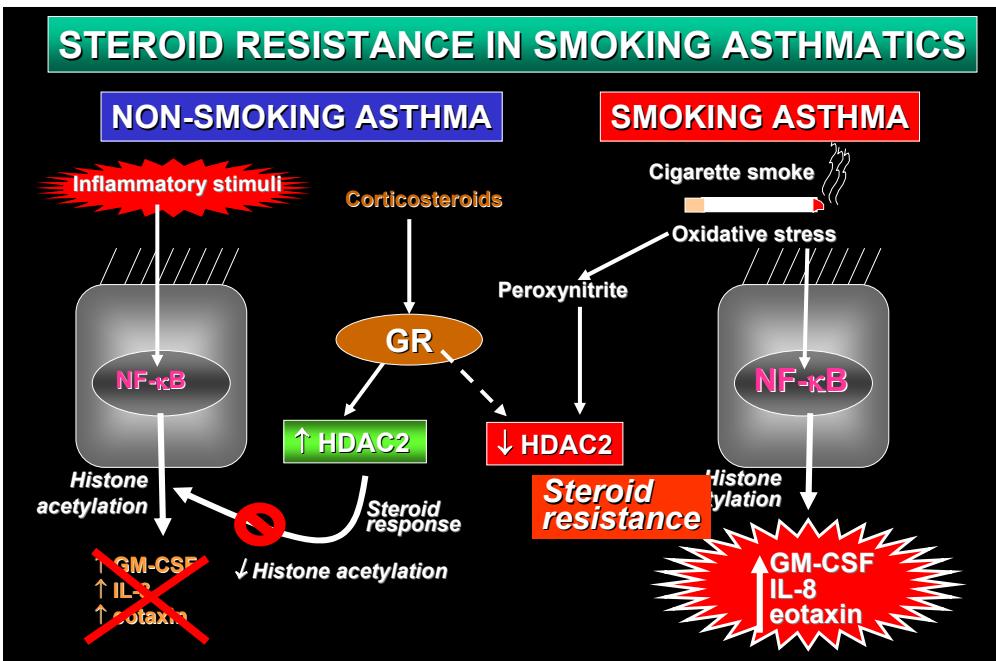


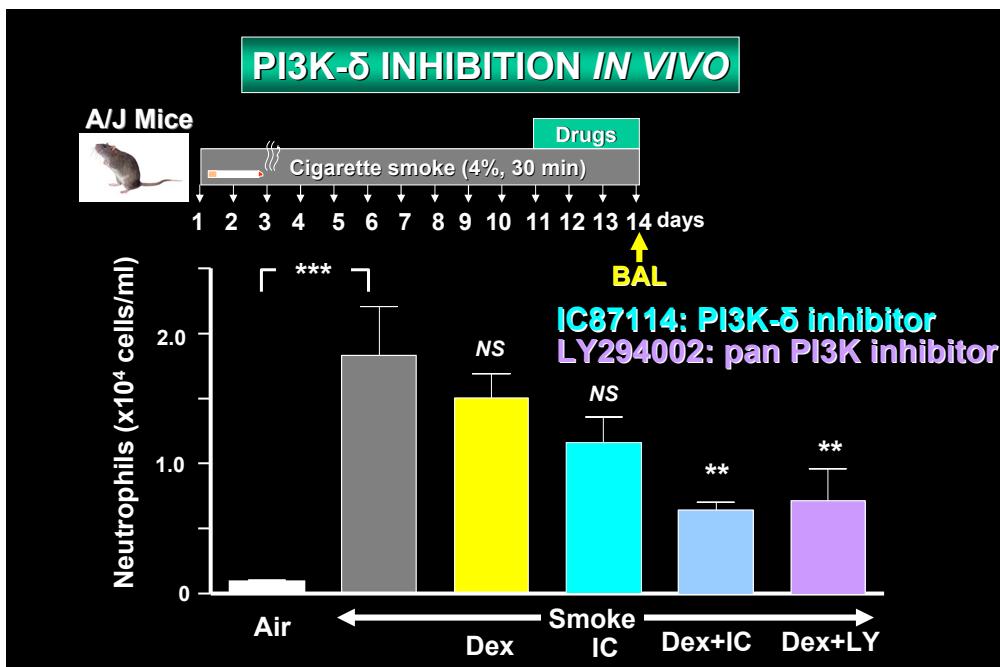
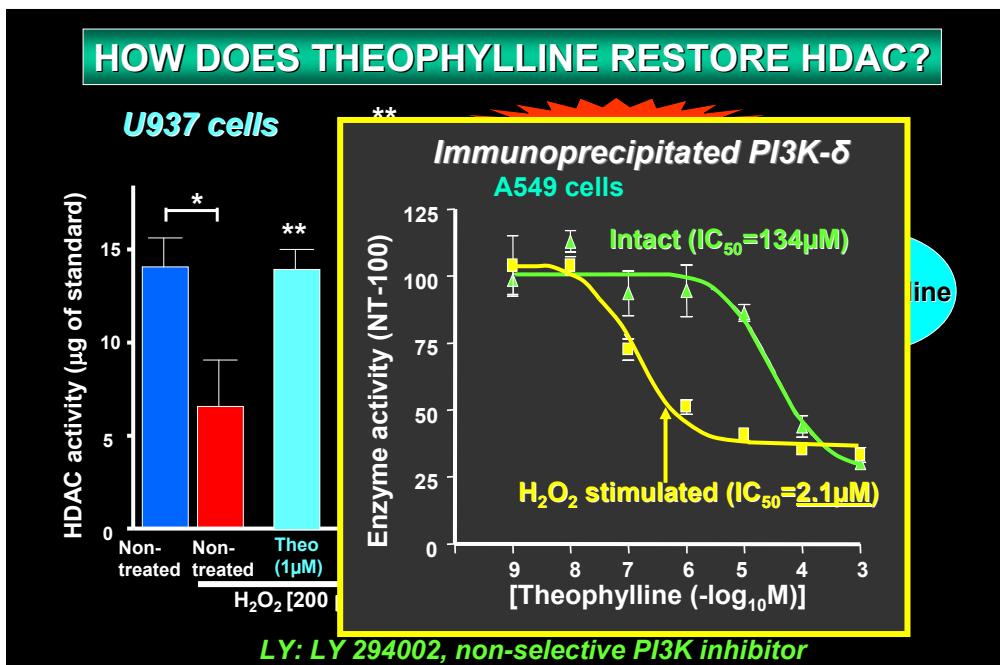


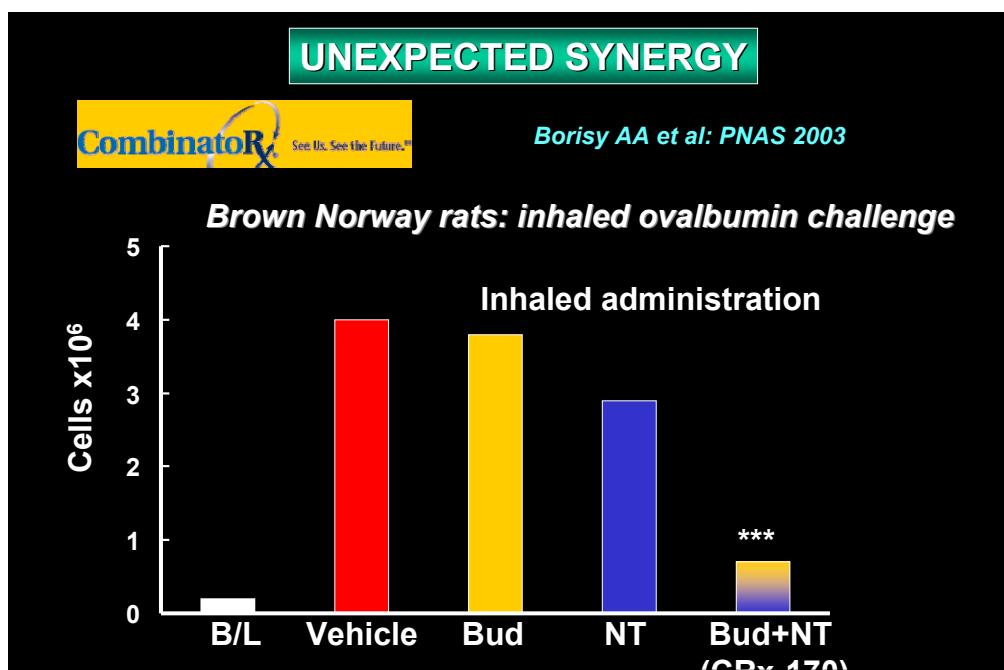
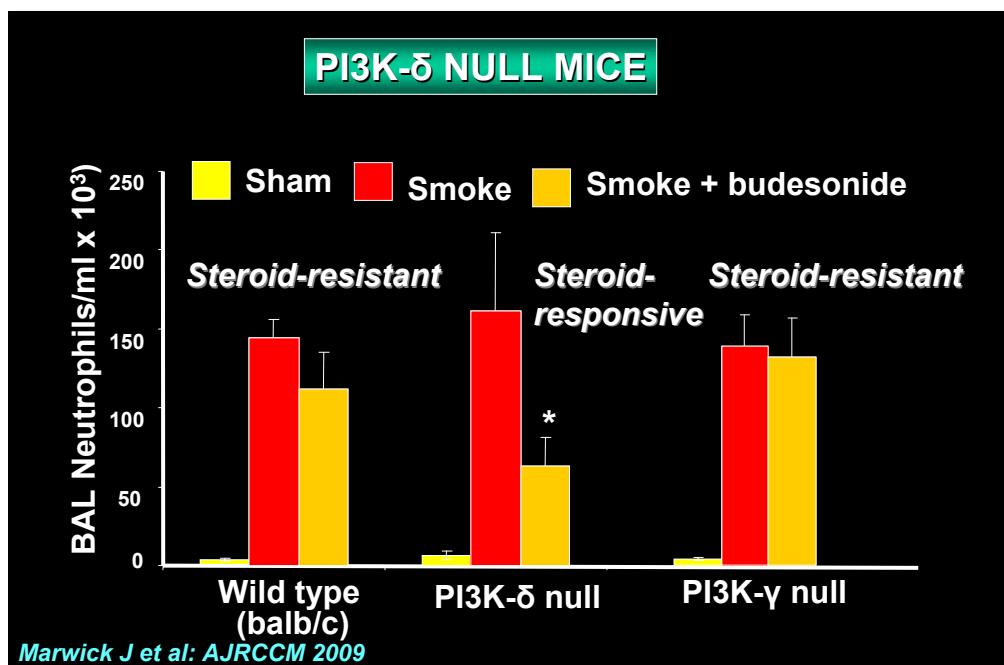


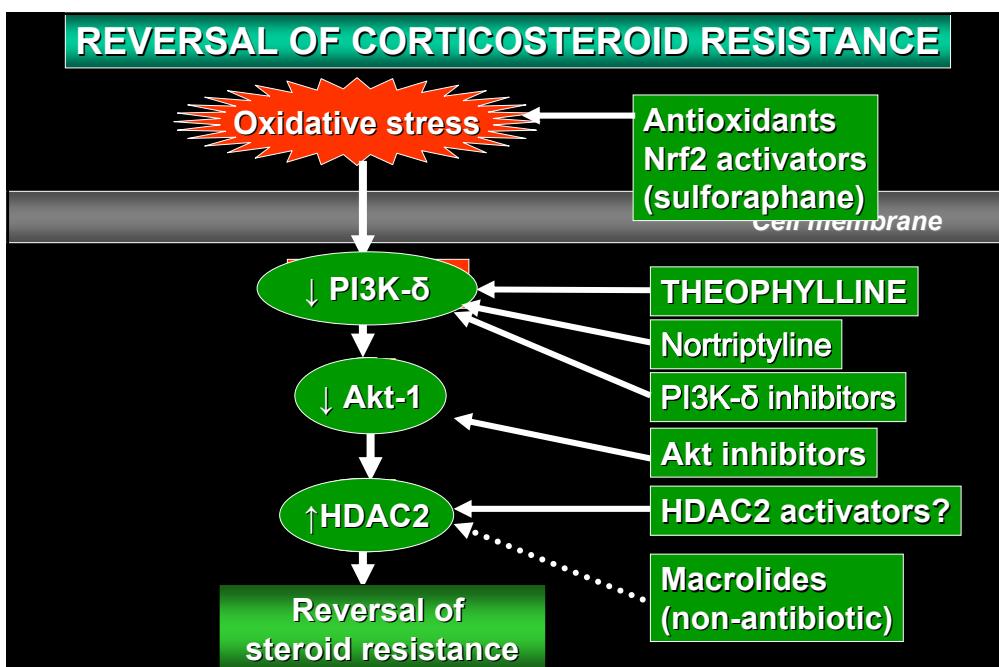
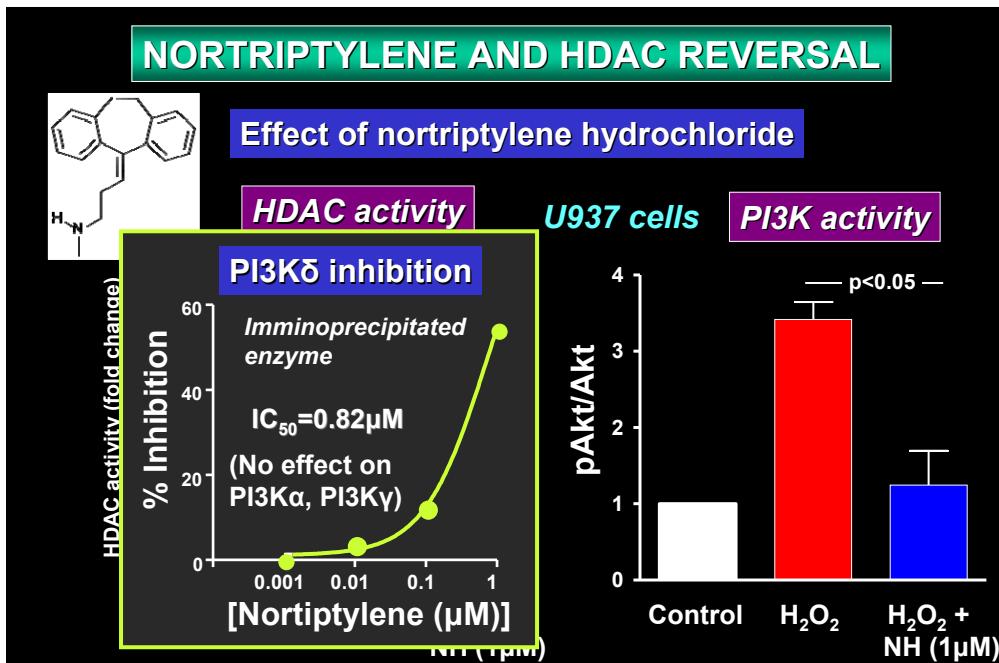


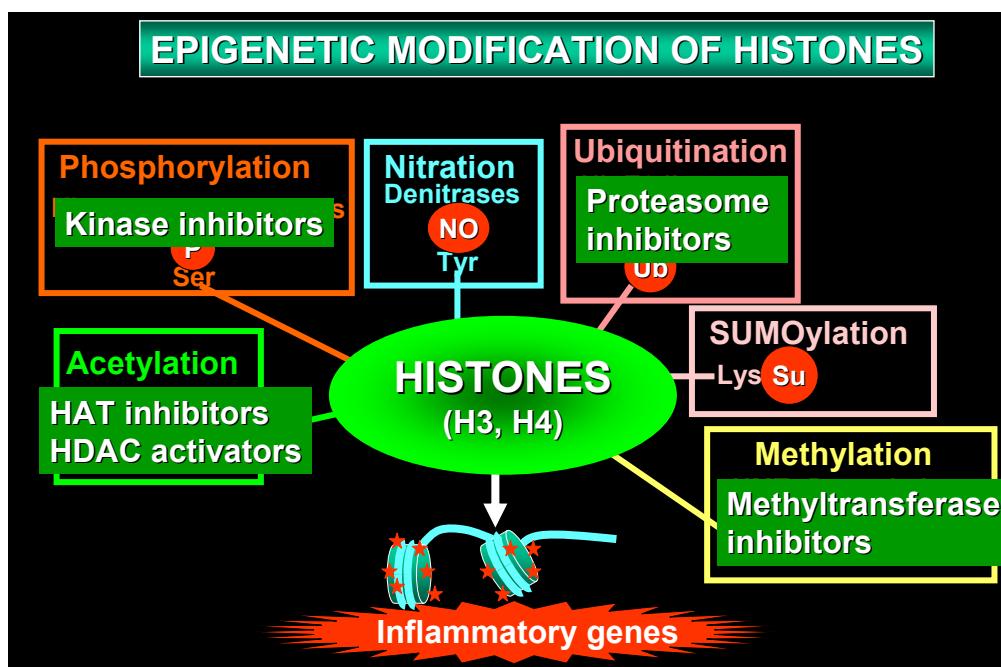
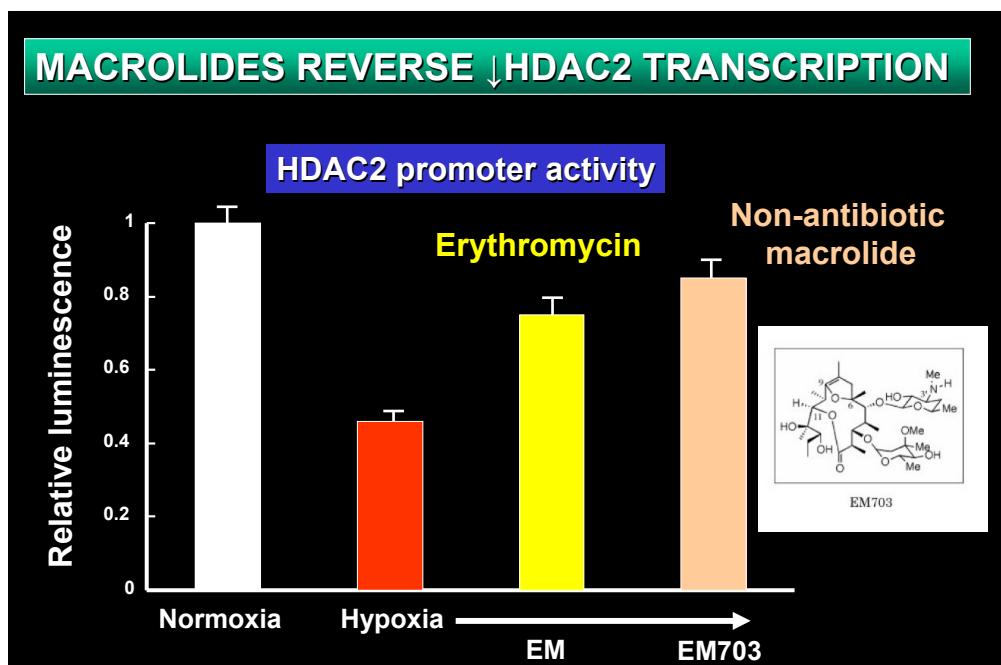


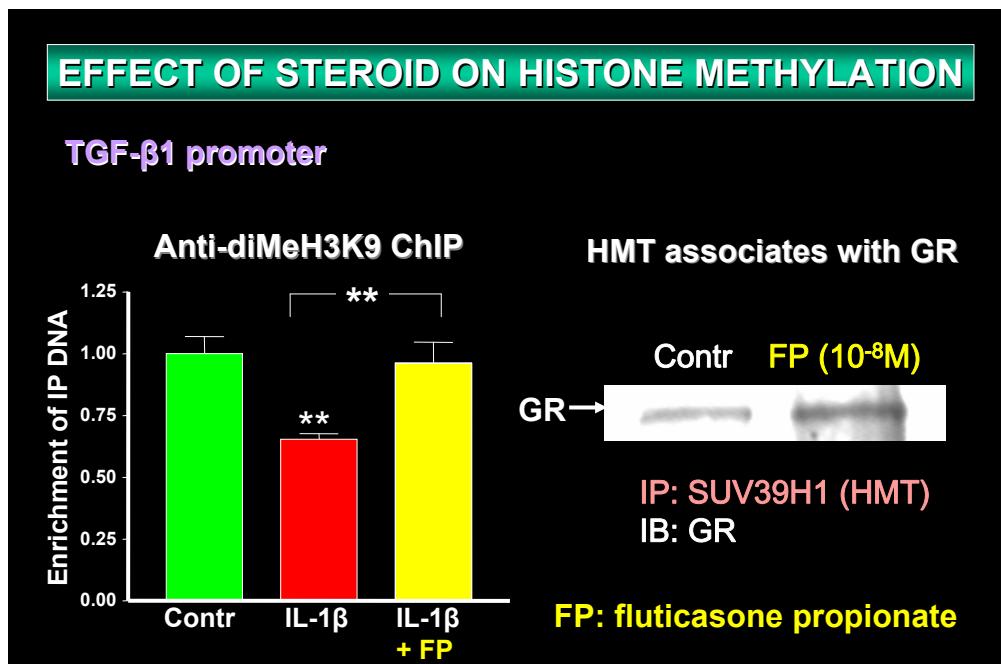
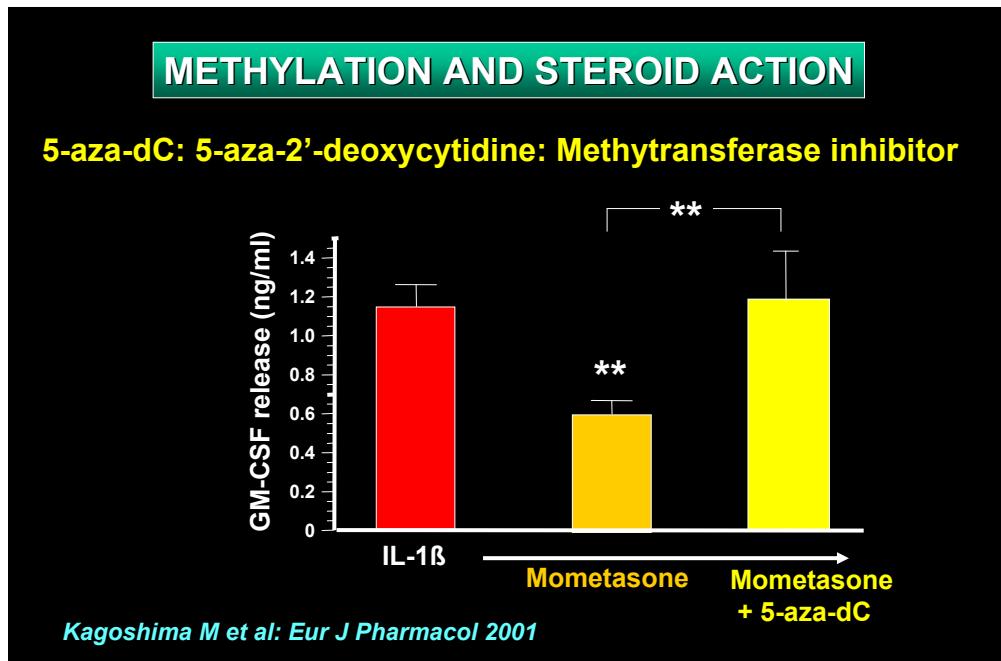


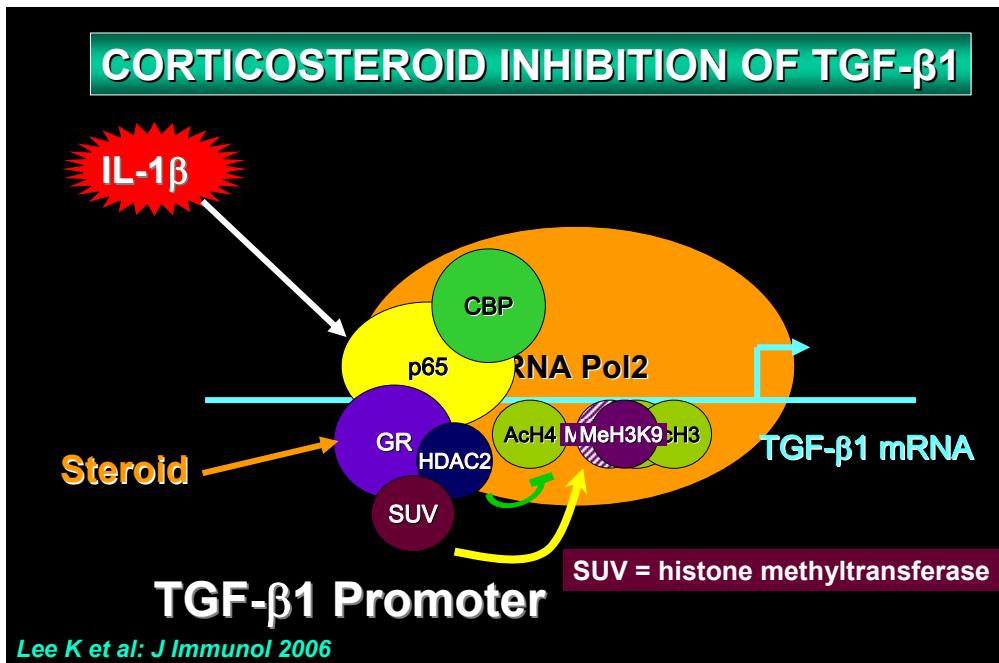












- CONCLUSIONS**
- Multiple histone modifications regulated by enzymes involved in regulation of inflammatory genes  
acetylation, methylation, phosphorylation, nitration, ubiquitination, sumoylation
  - HDAC2 recruitment mediates antiinfl effects of corticosteroids  
↓ in COPD: - due to oxidative/nitrative stress
  - HDAC2 activity restored by gene transfer, theophylline reverse corticosteroid resistance in COPD cells
  - Theophylline ↑ in HDAC2 mediated by PI3K $\delta$  inhibition
  - Histone methylation (H3K9) ↑ by corticosteroids  
HMT (SUV39H1) recruited by corticosteroids
  - New therapeutic approaches targeting epigenetic changes now possible

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