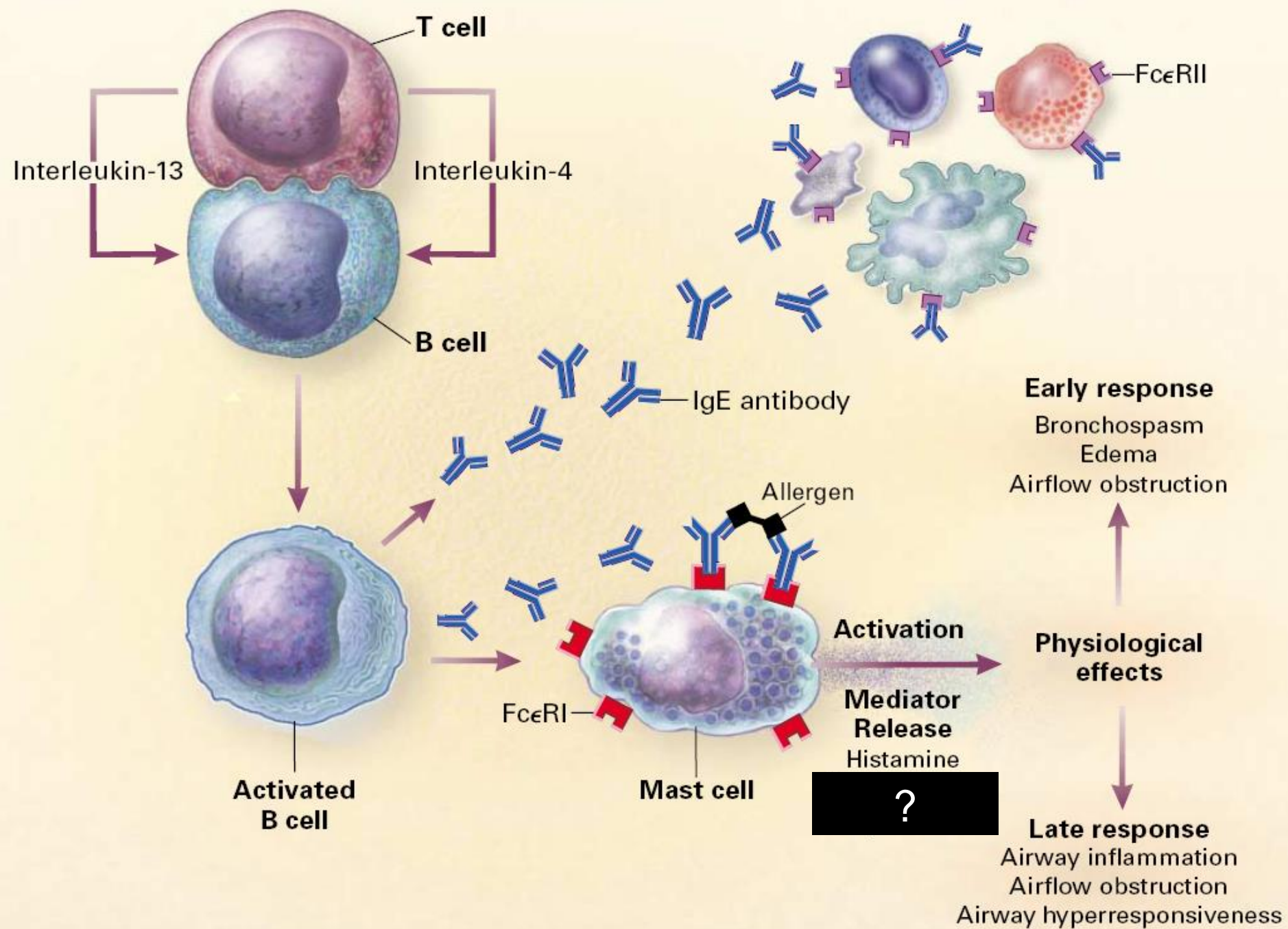
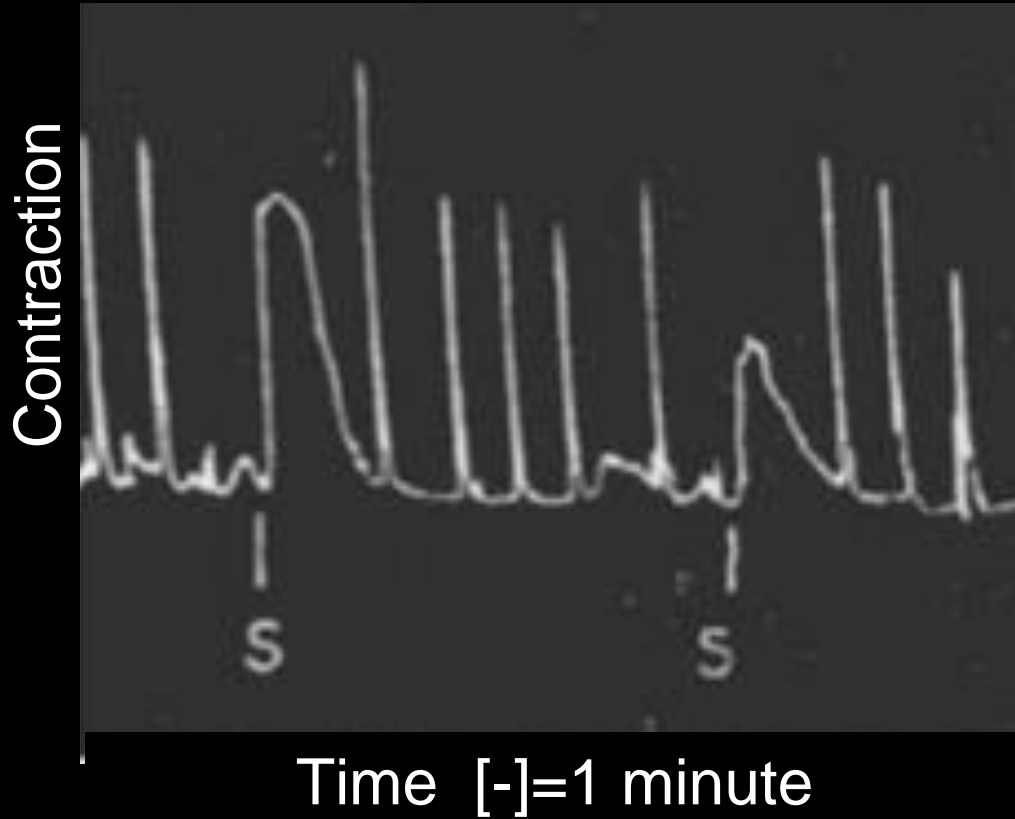
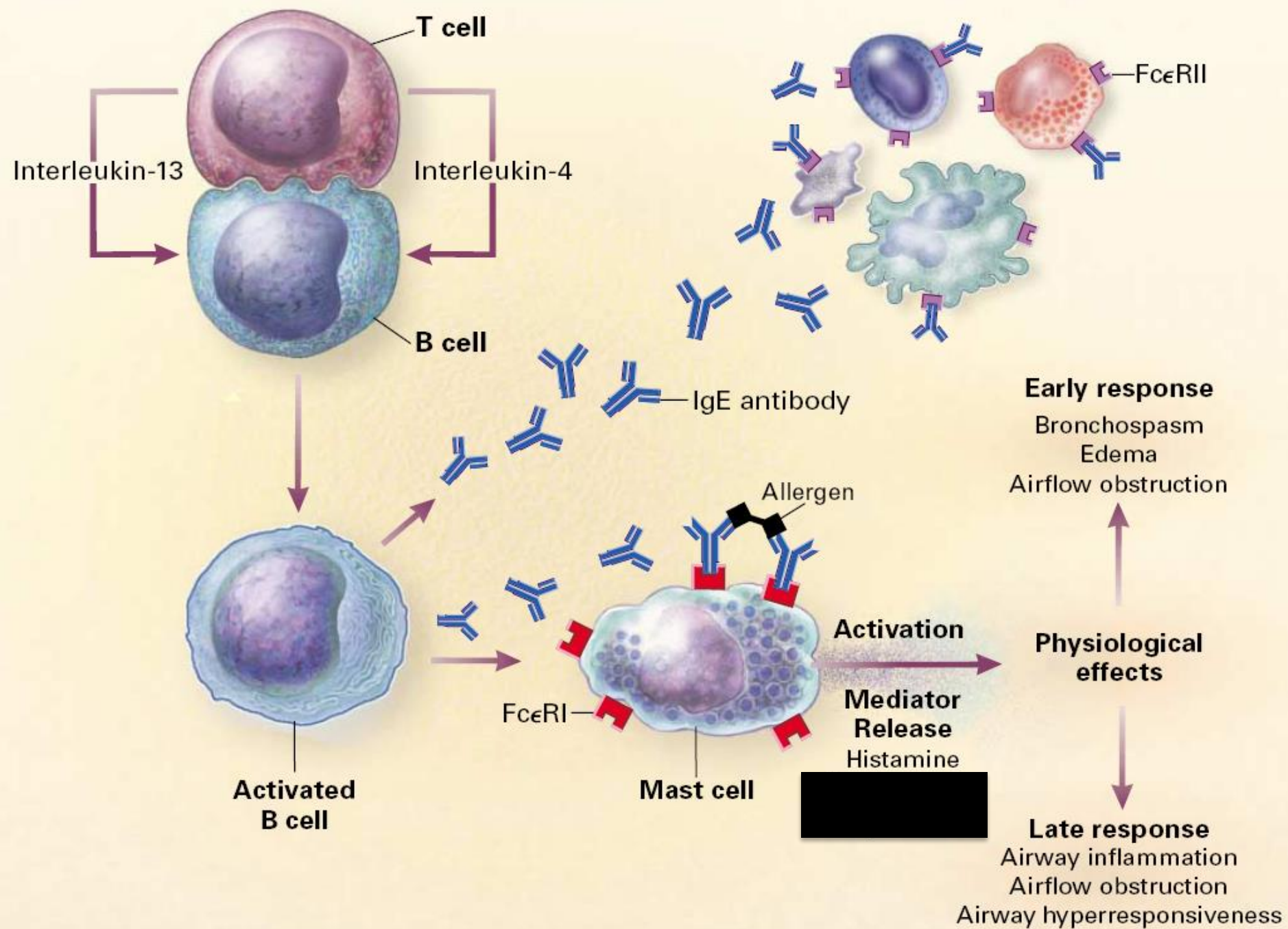


Evidence and Experience In Medicine



Kellaway and Trethewie-1938
Effects of Histamine and SRS on smooth muscle





Cytosol

Extracellular space

Chemotaxis

BLT receptor

Cytosolic phospholipase



The Nobel Prize in Chemistry 1990

"for his development of the theory and methodology of organic synthesis"



Elias James Corey

USA

Harvard University
Cambridge, MA, USA



The Nobel Prize in Physiology or Medicine 1982

"for their discoveries concerning prostaglandins and related biologically active substances"



Sune K. Bergström

🕒 1/3 of the prize

Sweden



Bengt I. Samuelsson

🕒 1/3 of the prize

Sweden



John R. Vane

🕒 1/3 of the prize

United Kingdom

Leukotriene E₄

airway muscle contraction

Eosinophil migration
Edema

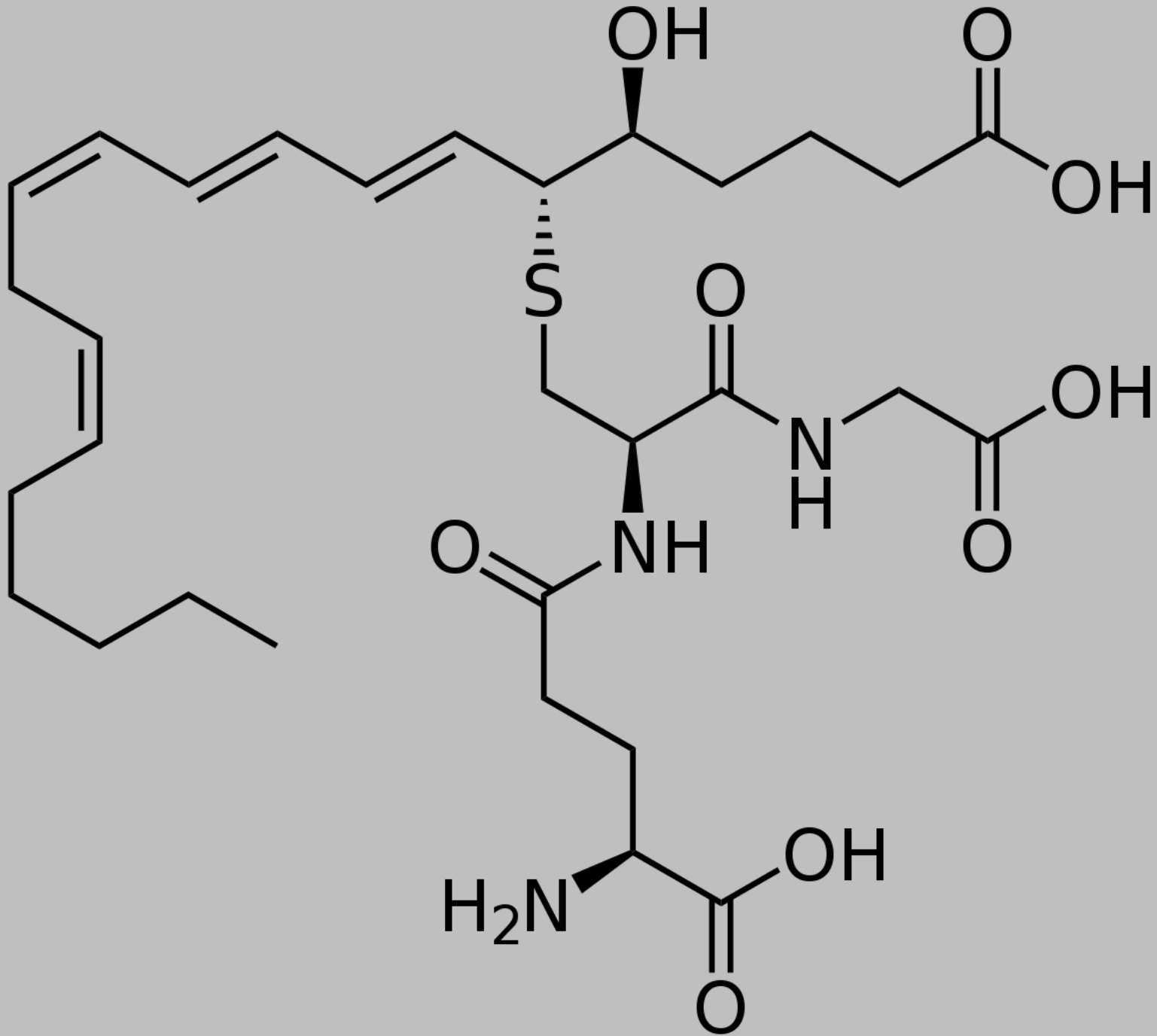
Nucleus

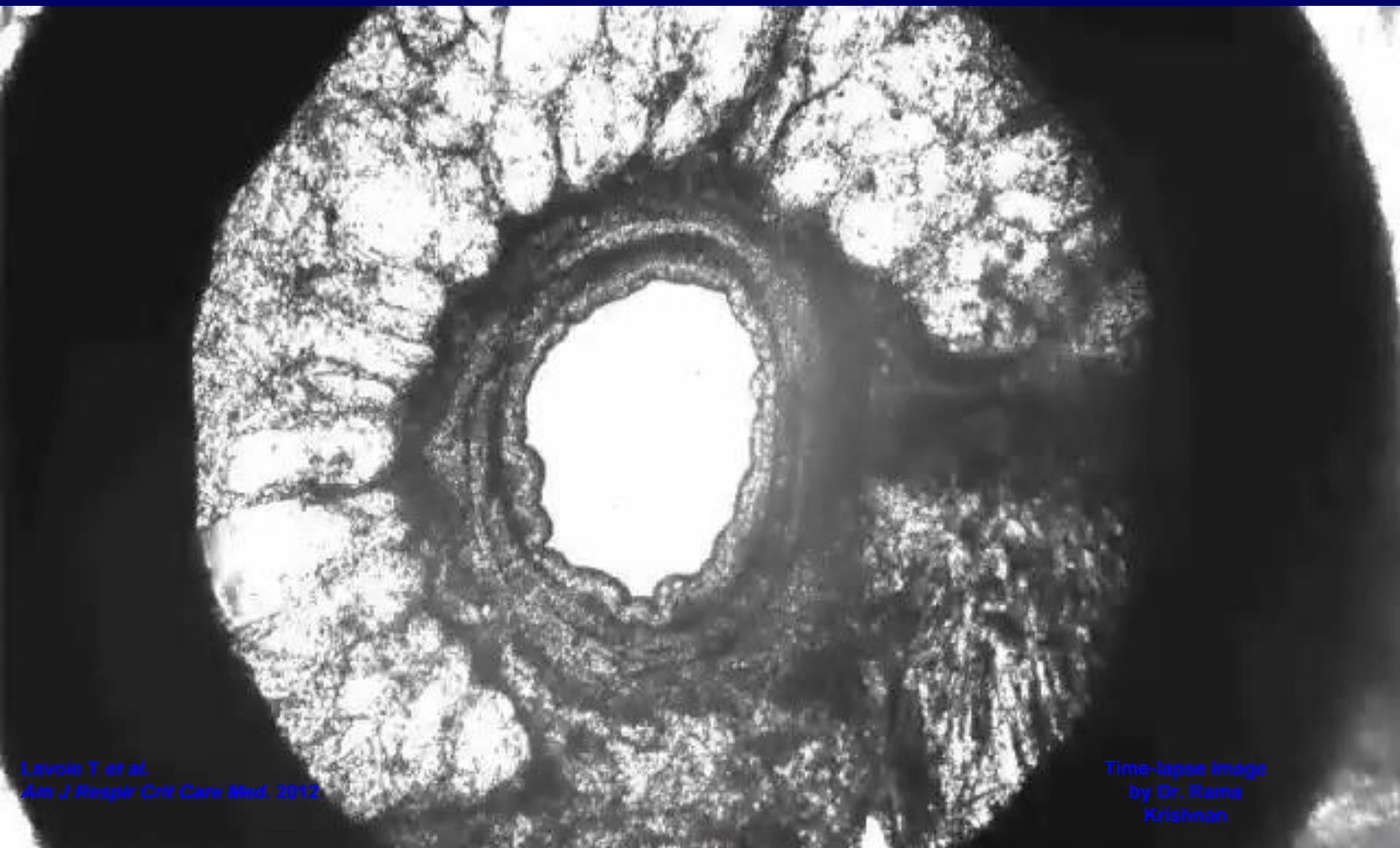
5-Lipoxygenase

Leukotriene synthase

Nuclear membrane

Leukotriene synthase





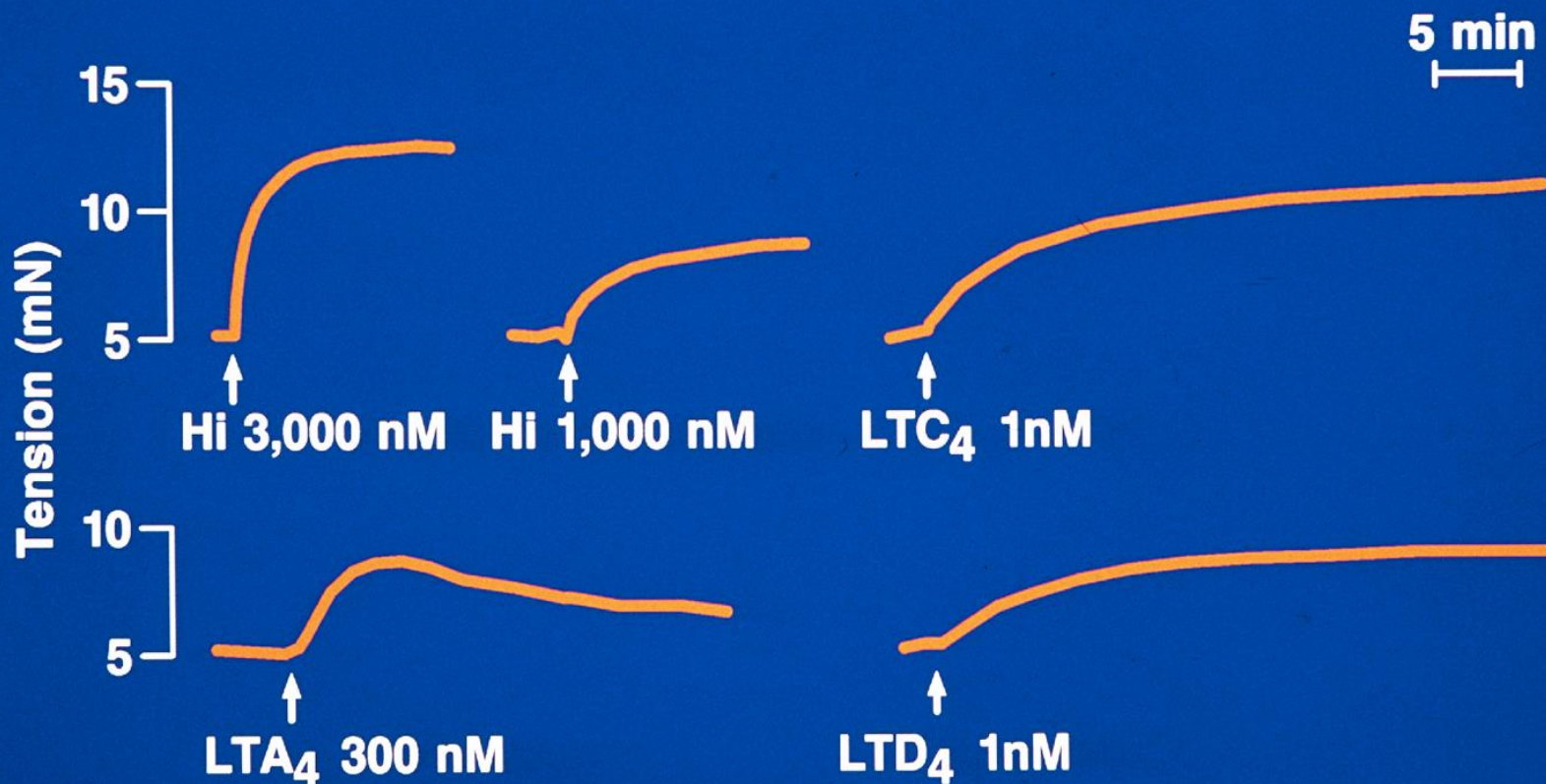
Lavoie T et al.
Am J Respir Crit Care Med. 2012

Time-lapse image
by Dr. Rama
Krishnan

Causality

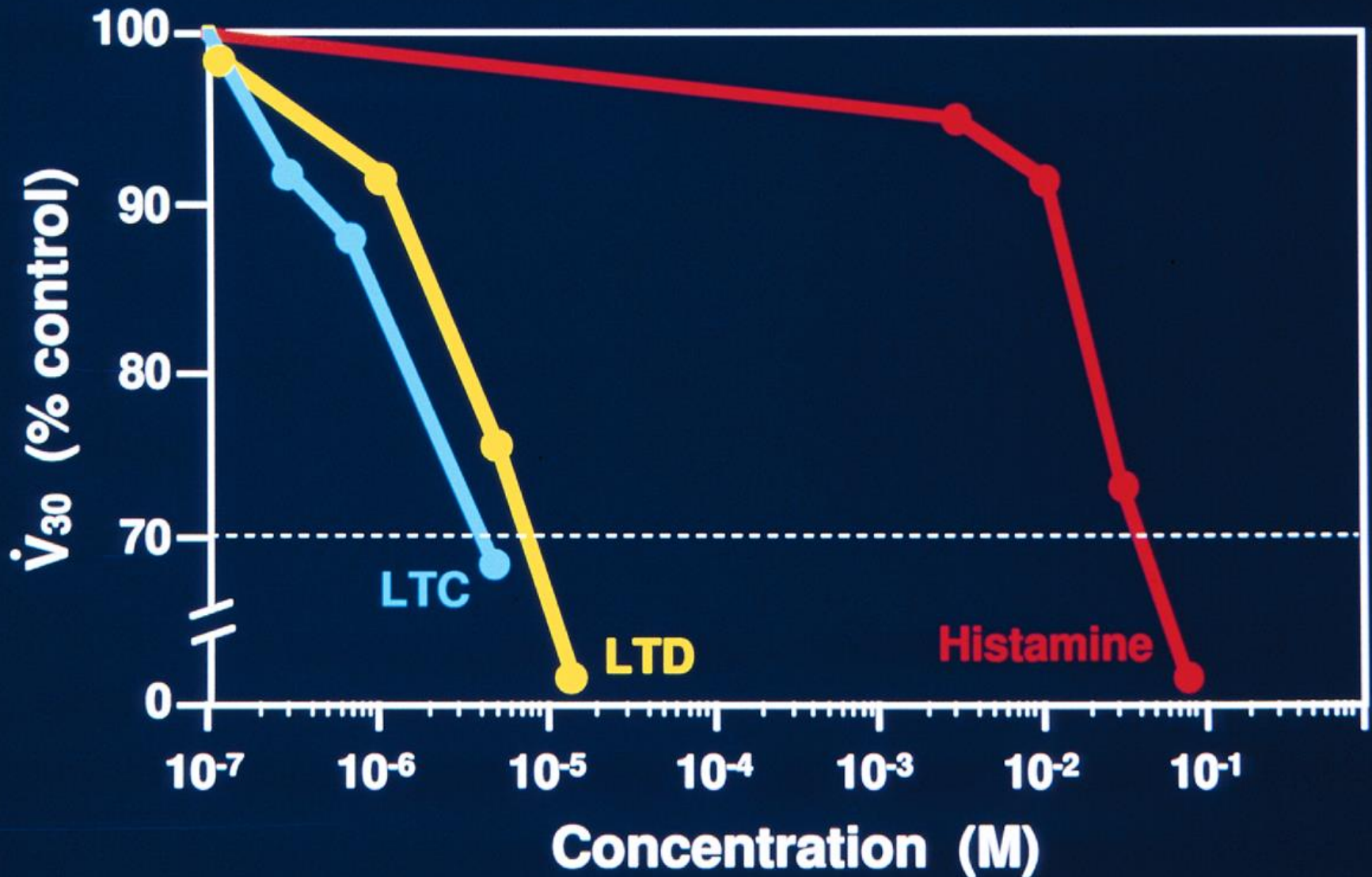
- Association between phenomenon of interest and outcome-epidemiology/plausibility
- Recovery of evidence of activity-clinical experiments
- Administration or activation leads to outcome-humans or animals
- Inhibition or augmentation leads to clinical resolution

Effects of LTs on Human Airways in vitro



(Dahlen et al., 1980)

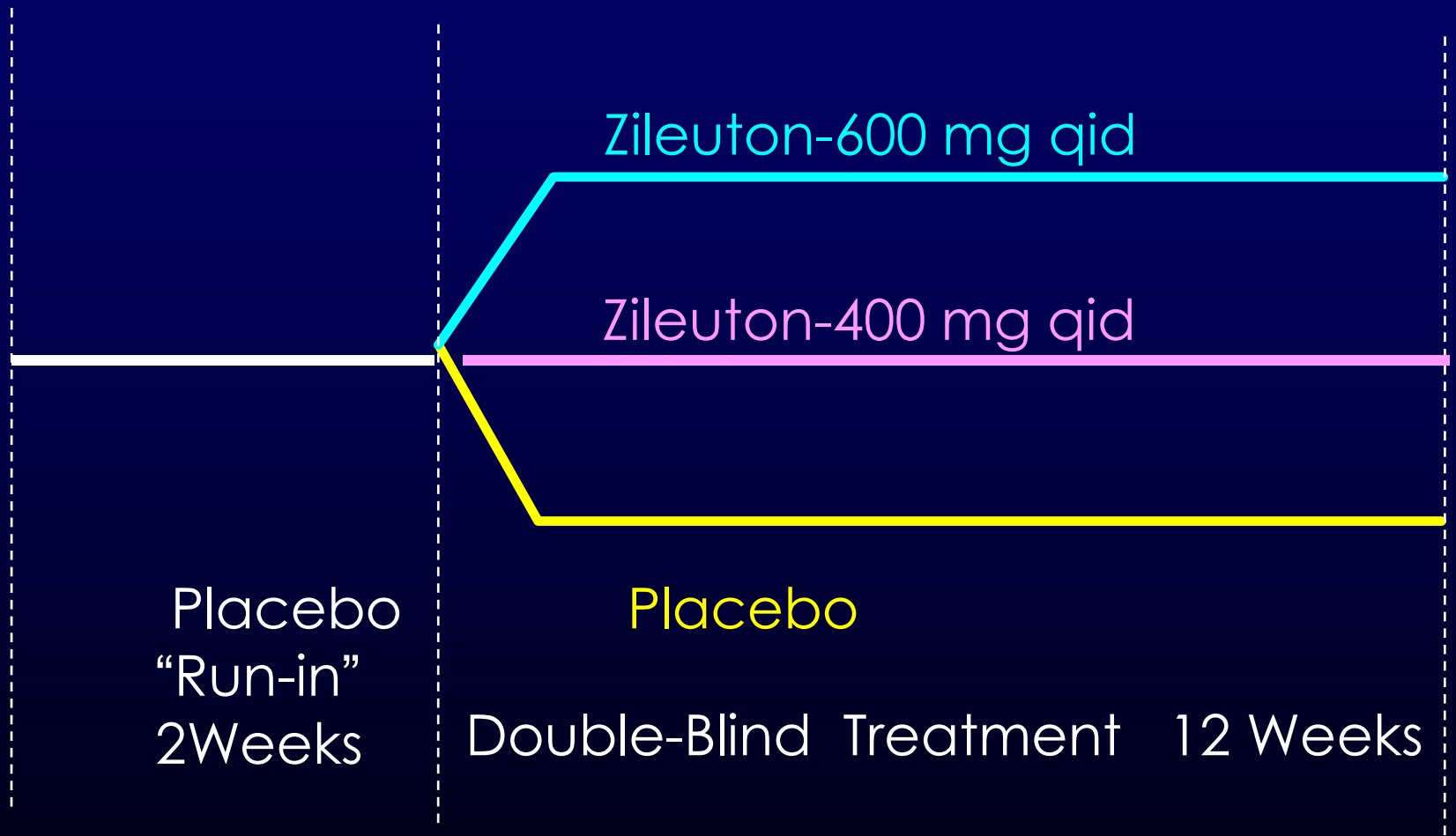
Cumulative Dose Response Subject JD



Causality

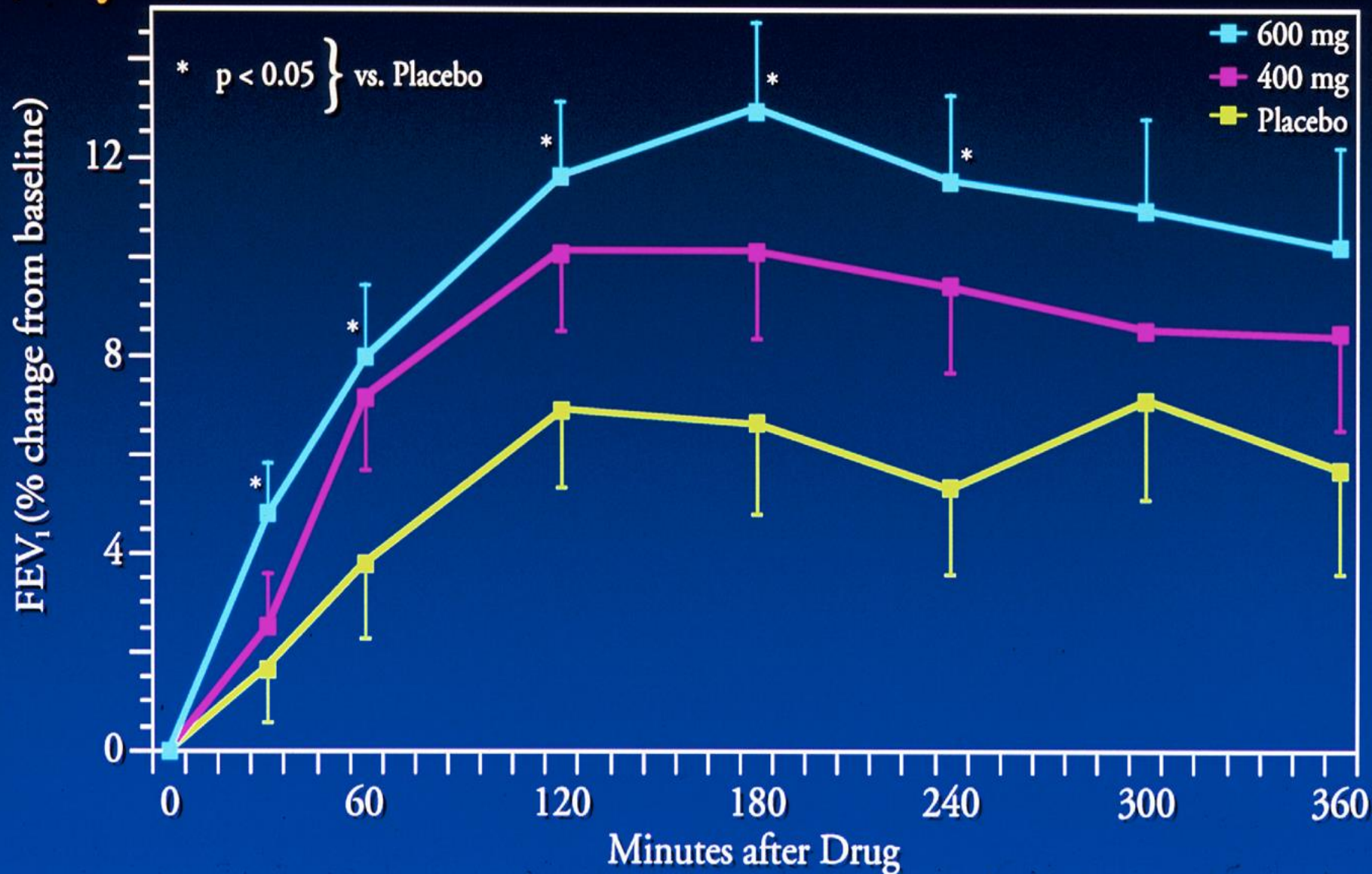
- Association between phenomenon of interest and outcome-epidemiology/plausibility
- Recovery of evidence of activity-clinical experiments
- Administration or activation leads to outcome-humans or animals
- Inhibition or augmentation leads to clinical resolution

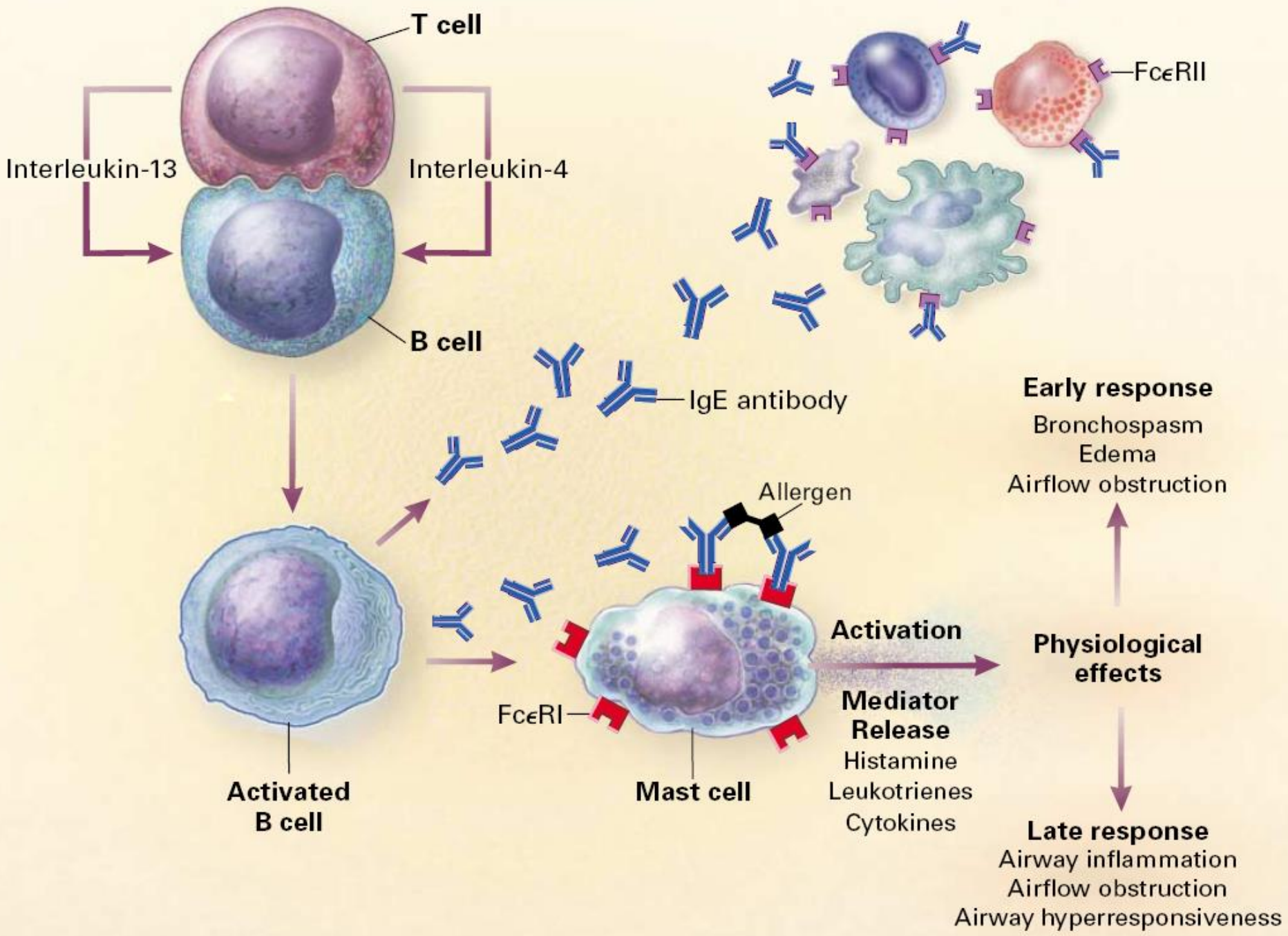
Zileuton-12 week trial



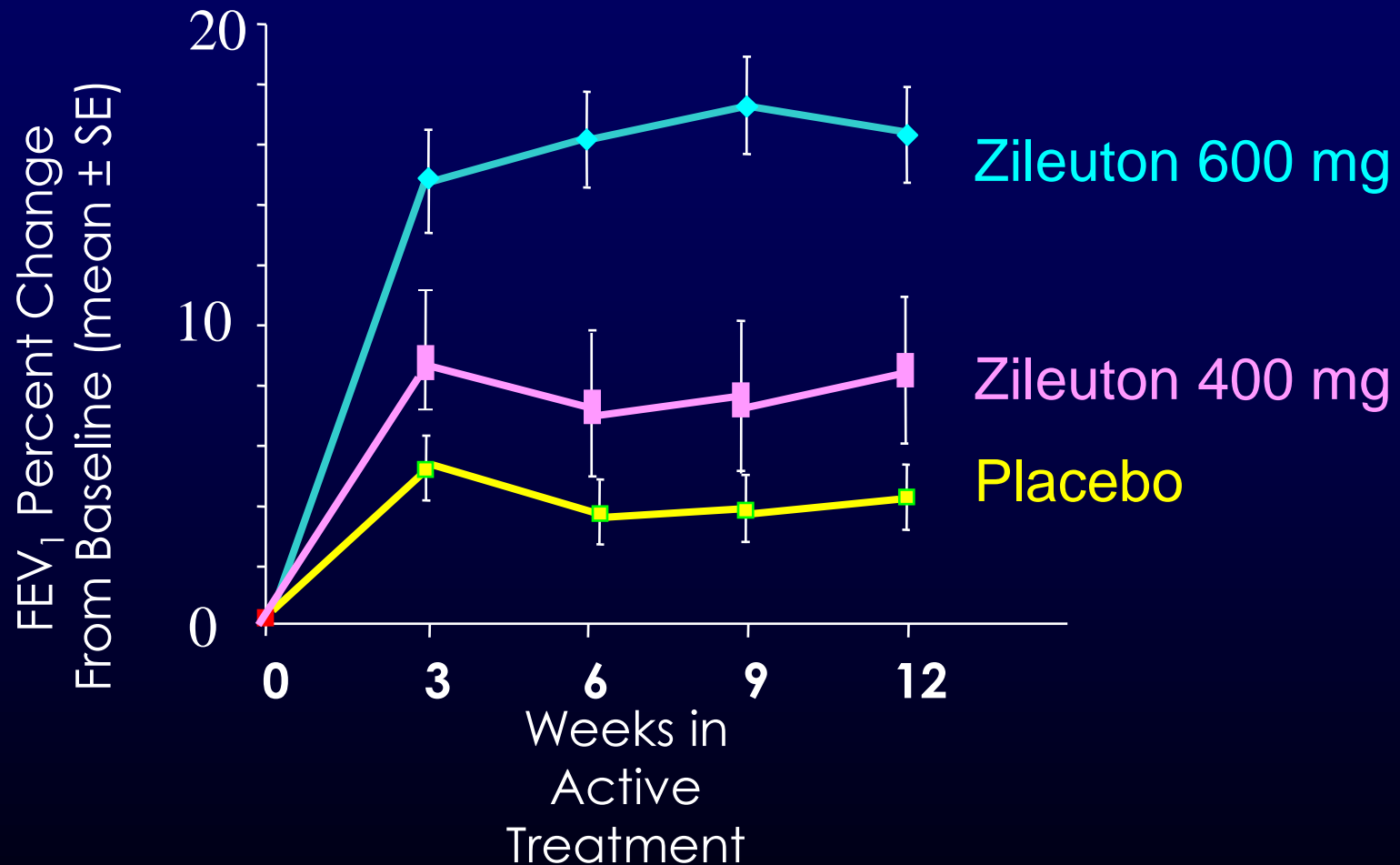
FEV1 was ~65% pred. in all groups

Acute Effect of Zileuton on FEV₁ (Day 1)





FEV₁ change after Zileuton



SINGULAIR®

(MONTELUKAST SODIUM)

ONE TABLET DAILY

10 mg
Tablets



Store at room temperature
15-30°C (59-86°F), protected from
moisture and light.



100% Recycled Paperboard
65% Post-Consumer Content



NDC 0310-0402-95

Patient Starter Kit

ACCOLATE®

ZAFIRLUKAST

Fourteen **20** mg tablets

Reducing

ZYFLOCR

(Zileuton) extended-release tablets, 600 mg

AVAILABLE NOW!

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 25, 2014

VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab
in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D.,
Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M.,
for the SIRIUS Investigators*

Run-in Period
(3–8 wk before
start of study)

Study Drug Administered

Primary
Efficacy
Outcome
(exit visit)



Wk	0	4	8	12	16	20	24	32
Visit	3	4	5	6	7	8	9	Follow-up

Visit 1

Visit 2

Optimization
phase

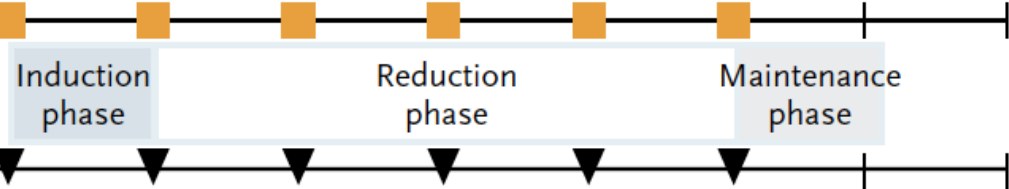
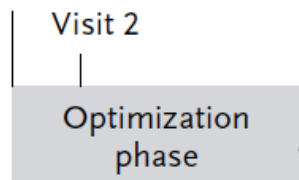
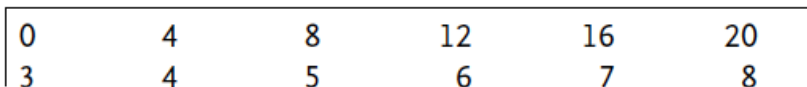
Induction
phase

Reduction
phase

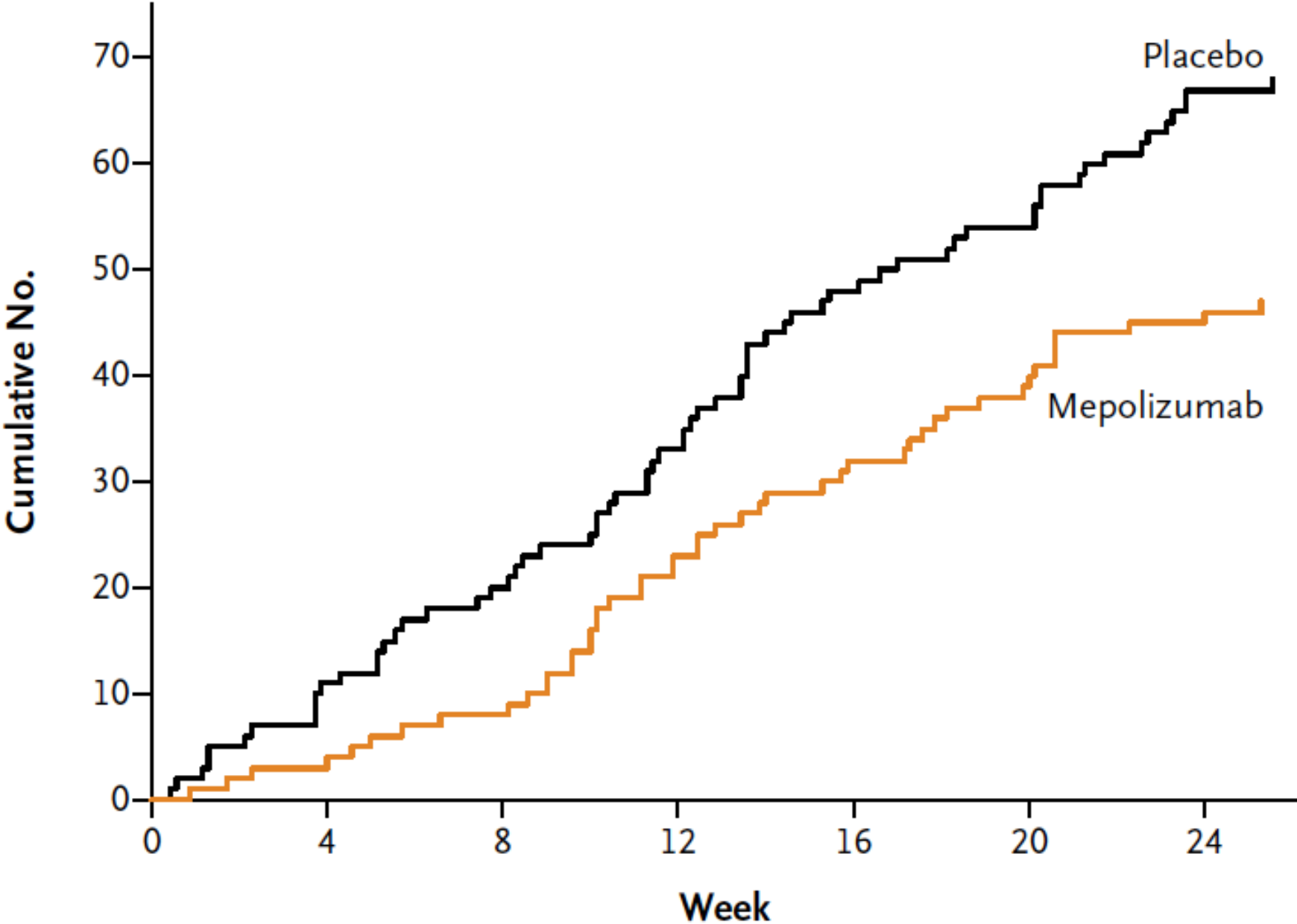
Maintenance
phase

■ Mepolizumab 100 mg,
subcutaneously every
4 wk

▼ Placebo subcutaneously
every 4 wk



B Asthma Exacerbations



ARTICLES | VOLUME 3, ISSUE 5, P355-366, MAY 01, 2015

Reslizumab for inadequately controlled asthma: results from two multicentre, parallel, placebo-controlled, phase 3 trials

Prof Mario Castro, MD • James Zangrilli, MD • Prof Michel Goldman, MD • Prof Guy G Brusselle, MD • Prof Philip Bardin, MD • et al. [Show more](#)

ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

ORIGINAL ARTICLE

Mepolizumab Treatment in Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Steven W. Yancey, M.Sc., and Pascal Chane for the MENSA Investigators*

ORIGINAL ARTICLE

Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

B Asthma Exacerbations

