

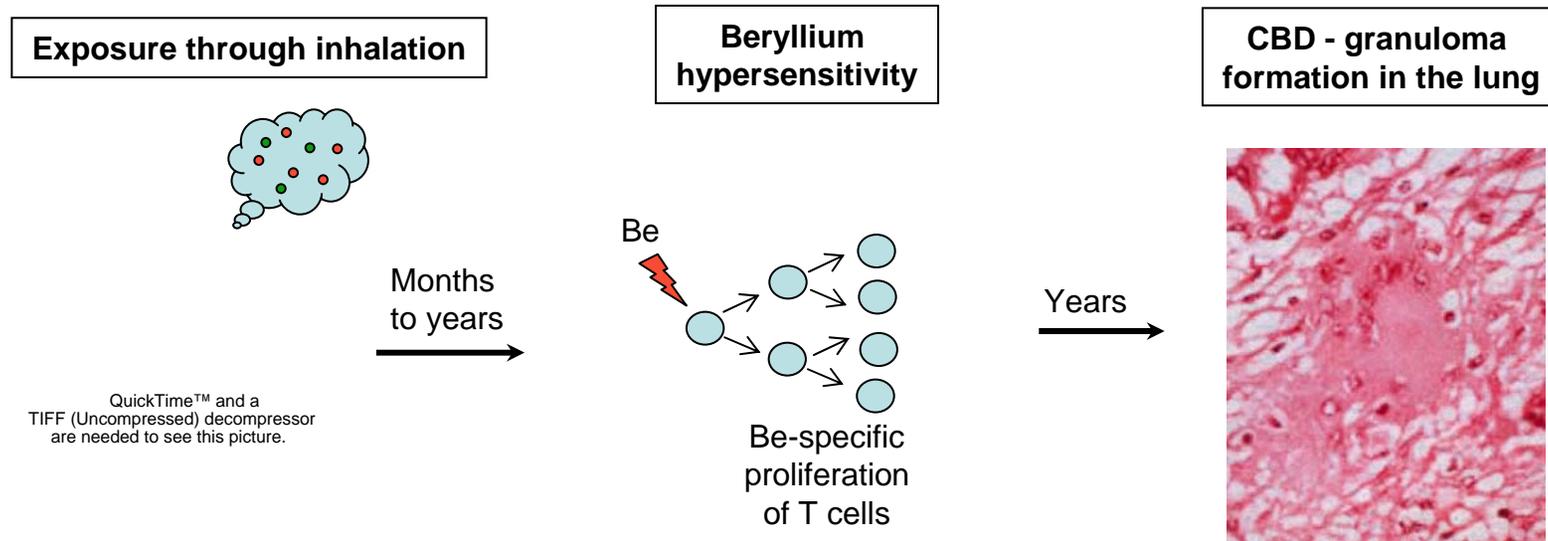
Bioscience

Innovation for Health and Security

Upregulation of I-CAM1 in response to beryllium exposure in small airway epithelial cells

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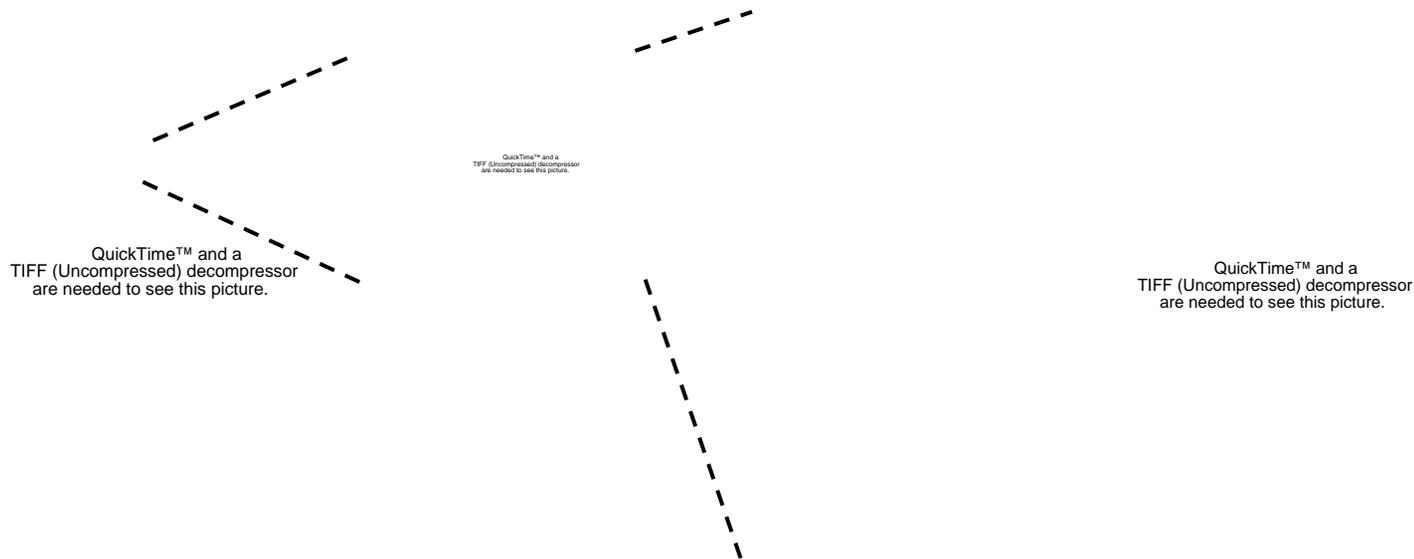
Study of beryllium exposure at Los Alamos National Labs



- Cases of CBD and beryllium hypersensitivity in LANL employees
- 1-8% current and retired workers exposed to Be have hypersensitivity, and 42-83% of these have CBD

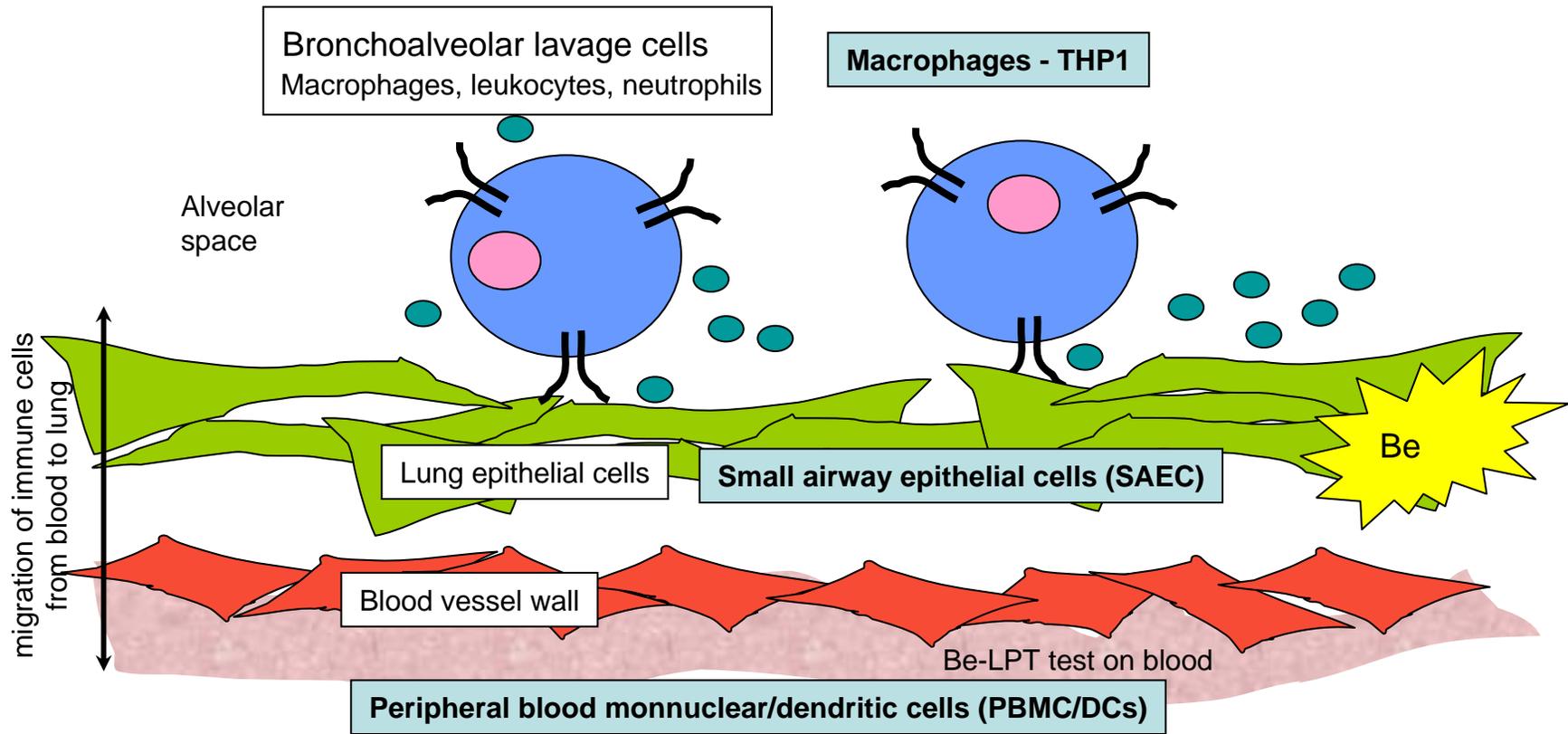
Inhalation of airborne particles into the lung

Alveolar structure in the lung



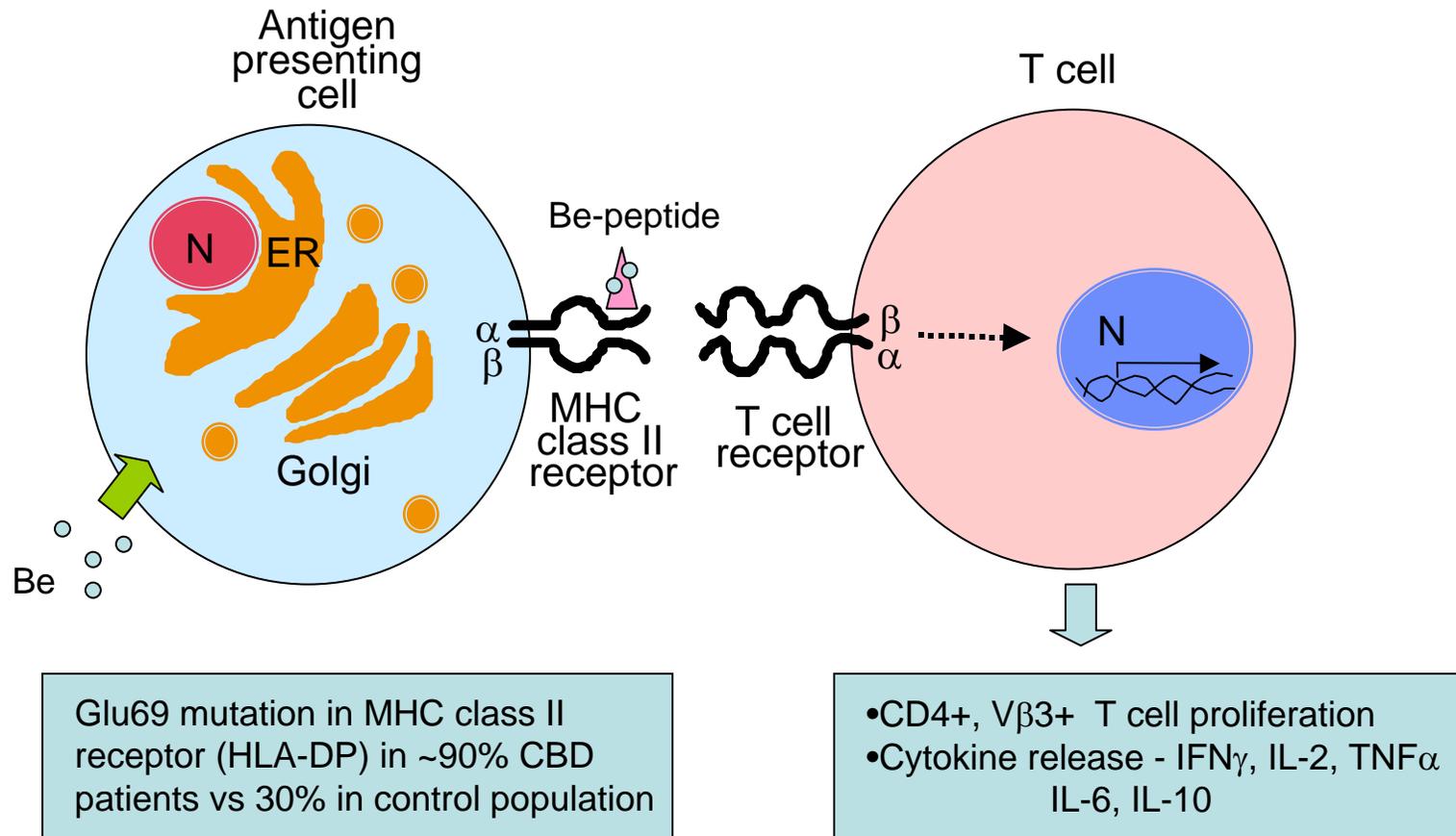
- Human lung:**
- first physical and immunological line of defense against airborne particles
 - juxtaposition between lung airway passages and circulatory system
 - 300 million alveoli, alveoli surface is 100 m²

Immune response to antigen exposure in the lung



- Upregulation of Th1 pro-inflammatory **cytokines** at site of inflammation to stimulate host immune response

Beryllium stimulation of the host immune response



Microarray analysis of Be-stimulated PBMC/DCs

RNA isolated from BeSO₄ and Al₂(SO₄)₃ cells

Reverse transcription

cDNA synthesis

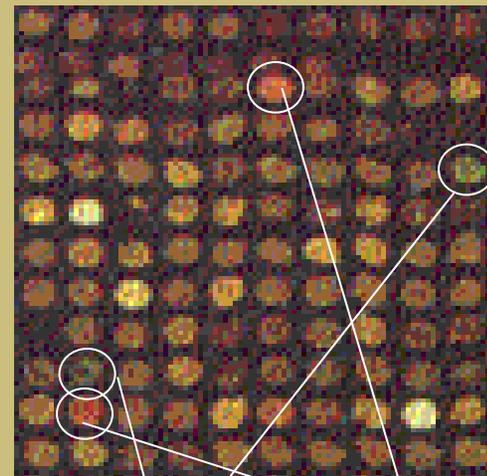
+Cy3, Cy5

Couple fluorescent dye to cDNA



Combine labeled cDNAs and hybridize to arrays

- 12,000 or 24,000 array produced using human cDNA library from Research Genetics (Cary Lab)



upregulated

downregulated

Upregulation of chemokines and cell adhesion gene expression in PBMC/DCs in response to Be

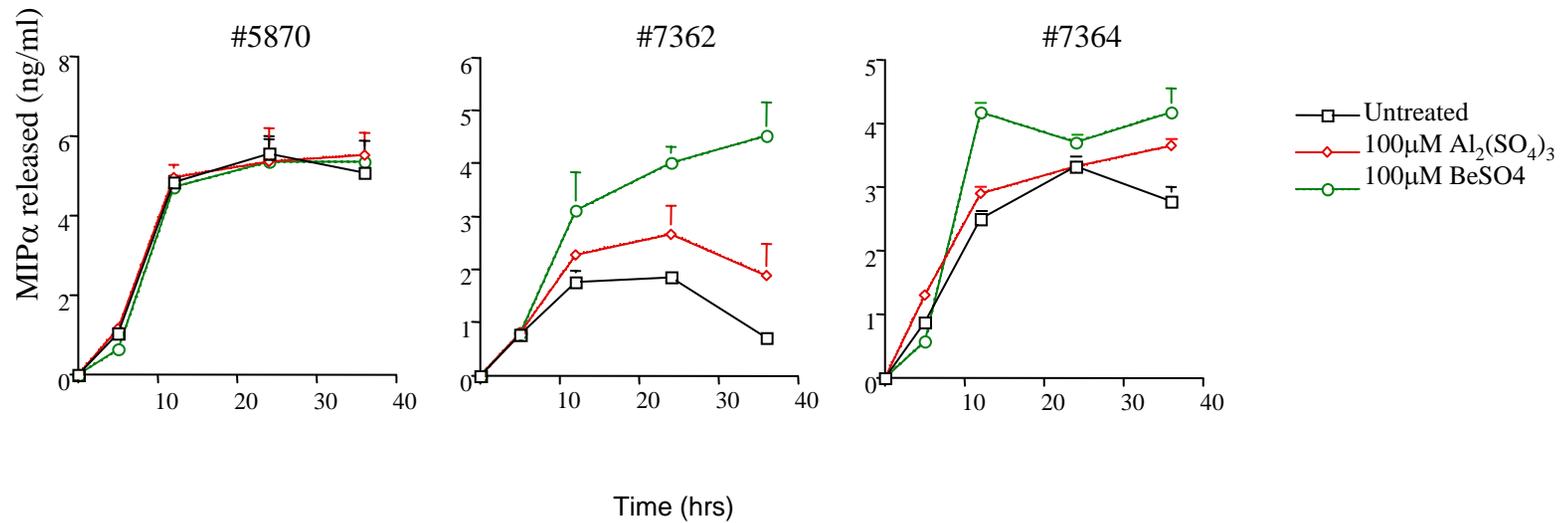
Selection of upregulated genes in Be-stimulated PBMC/DCs using microarray – 2x or higher in at least 4/5 arrays

Genbank	Gene	Fold increase	
H62864	MIP-1 β	3.79	} chemokines (chemotactic cytokines)
W42723	GRO1	4.55	
W46900	GRO1	2.86	
AA935273	GRO3 – MIP-2 β	6.34	
AA873792	Rantes	3.29	
AA677522	MIP-1 α	3.56	
W45275	CD44	5.17	} cell adhesion receptors
AA037229	Integrin β 3	2.36	

Hong-Geller, E., Pardington, P., Cary, R., Sauer, N., and Gupta, G. (2006) Chemokine regulation in response to beryllium exposure in human peripheral blood mononuclear and dendritic cells. *Toxicology* 218: 216-28

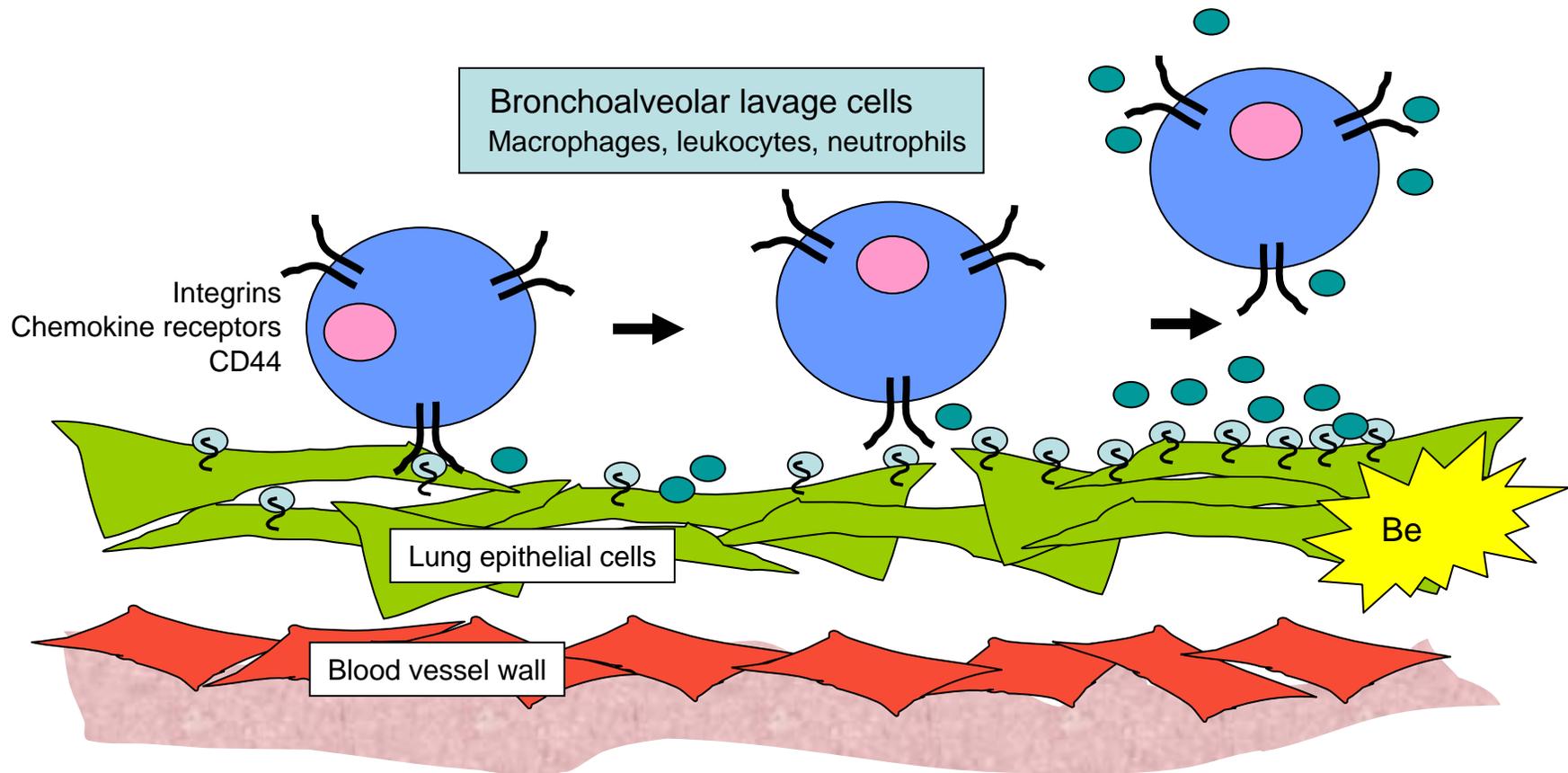
Hong-Geller, E and Chaudhary, A. (2007) Chemokine function in granulomatous lung disease. *Progress in Chemokine Research* (Nova Publishers).

Beryllium stimulates MIP α release in PBMC/DC model



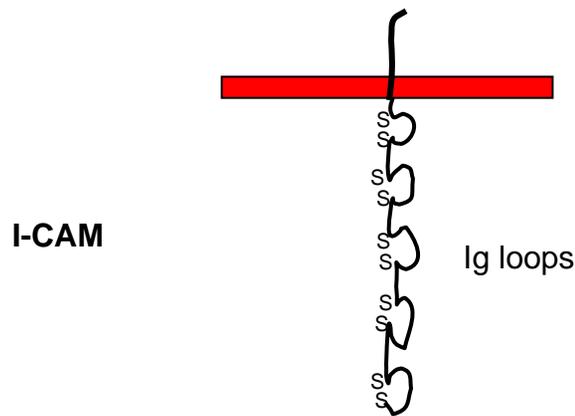
•standard sandwich ELISA assay

The role of cell adhesion in host immune response



- Release of **chemokines** at sites of inflammation to chemoattract immune effector cells
- Ⓢ Upregulation of **cell adhesion proteins** on lung epithelial cells (e.g. I-CAM, selectins)

I-CAM (intercellular adhesion molecule) is a cell adhesion receptor



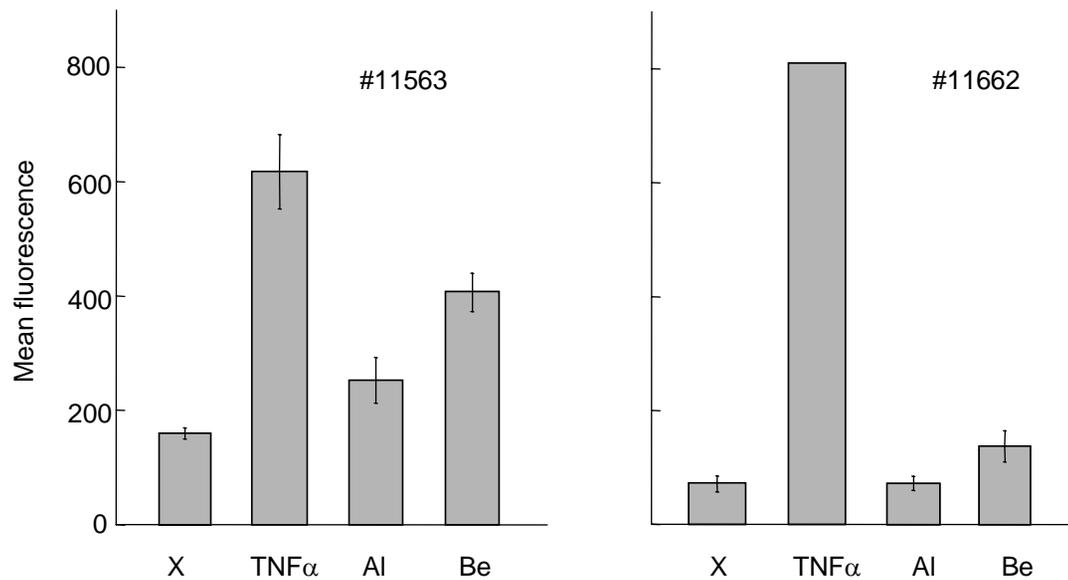
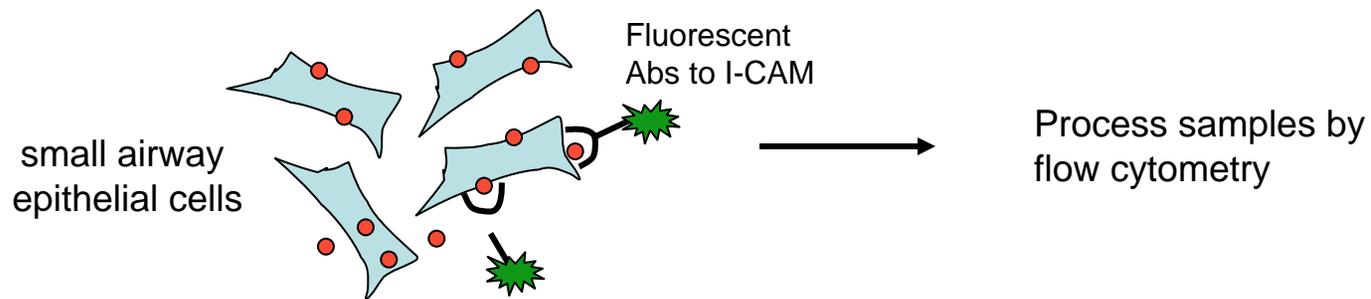
I-CAM:

- transmembrane, glycosylated receptor
- expressed in a wide variety of cells, from immune effector to epithelial cells
- function in cell-cell adhesion
- associated with multiple inflammatory diseases including those of the lung (e.g. asthma)
- upregulation in response to cytokines and pathogen infection during inflammation

Integrin β 2

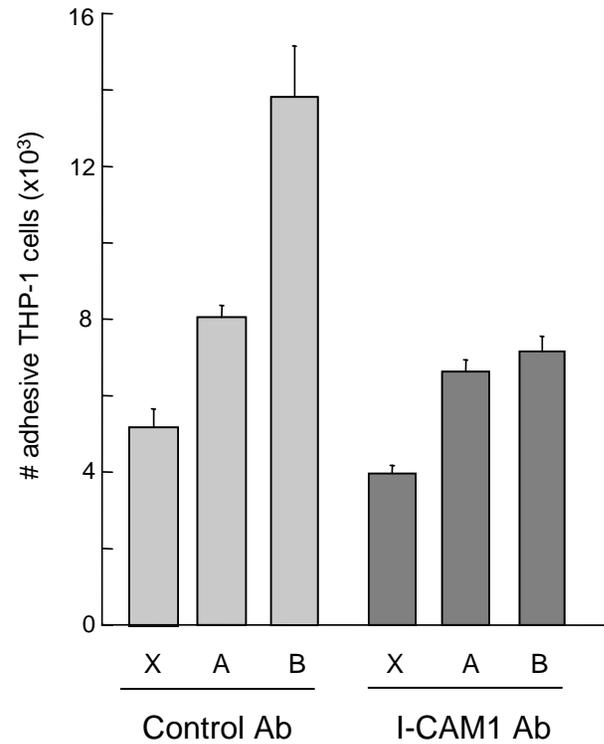
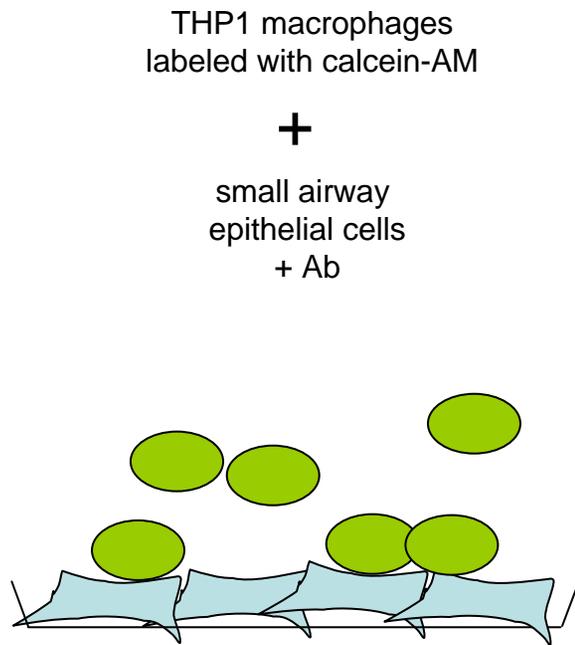
QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Detection of I-CAM on surface of SAE cells



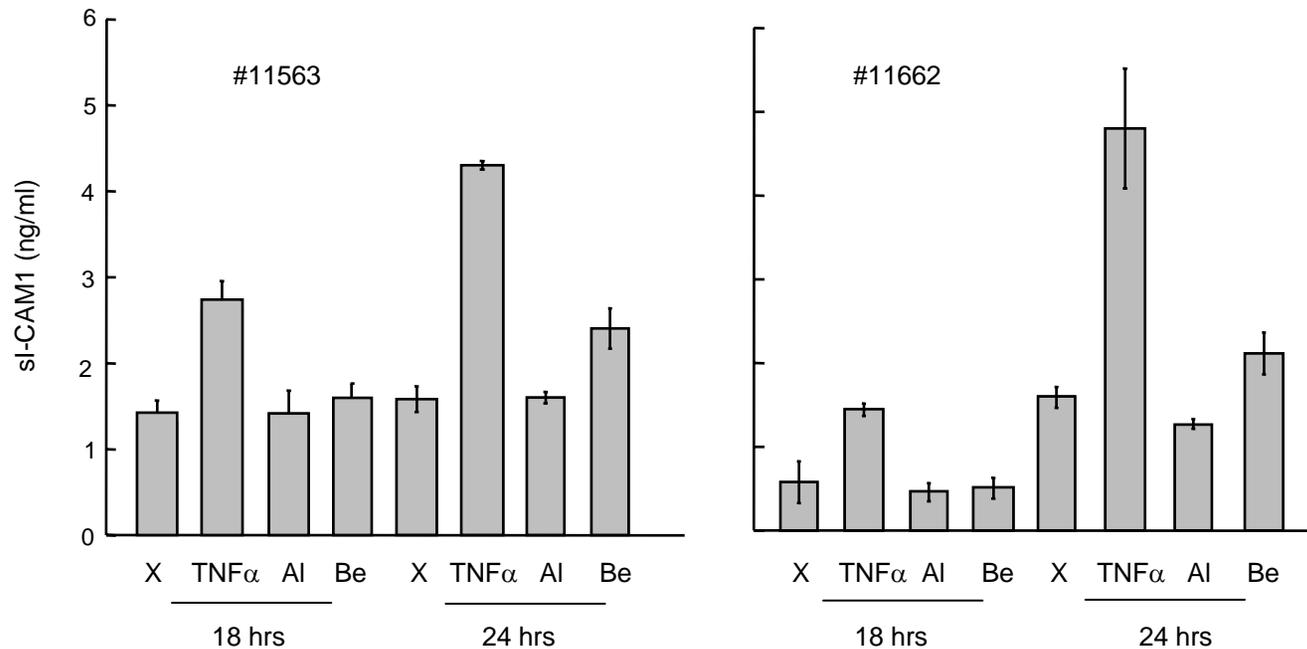
Rodriguez S, Kunde YA, McCleskey, TM, and Hong-Geller E. (2008) Upregulation of I-CAM1 in response to beryllium exposure in small airway epithelial cells. *Toxicol. Lett.* 179: 140-147.

Be stimulates cell adhesion properties in SAE cells



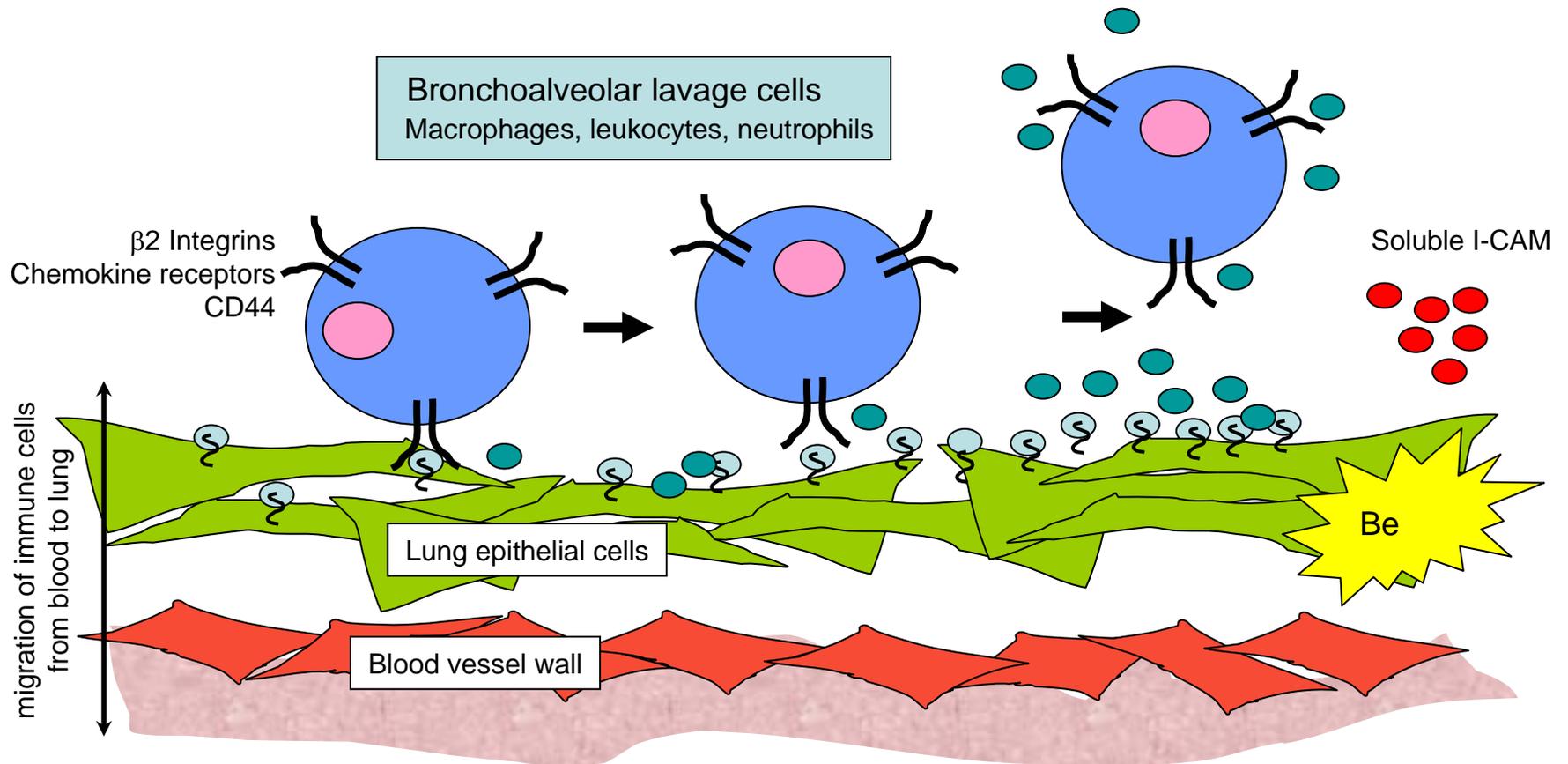
Be induces release of soluble I-CAM (sI-CAM)

- sI-CAM:
- levels in body correlate with intensity of clinical condition, seen in inflammatory diseases
 - acts as competitive inhibitor, binds to integrins on macrophages to reduce adhesive properties
 - induces intracellular signaling pathways in macrophages, activation of immune cells
 - associated with enhancement of lung injury



- standard sandwich ELISAs using I-CAM antibodies

Immune response to Be exposure in lung epithelial cells



- Secretion of cytokines and chemokines at sites of inflammation
- ⌘ Upregulation of **cell adhesion proteins** by lung epithelial cells during inflammation (e.g. I-CAM)
- Release of soluble I-CAM by lung epithelial cells

Acknowledgements

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