•**Eosinphils** Modulate Tumor Microenvironment By Oxidizing **DAMPs** From Necrotic **Tumor**

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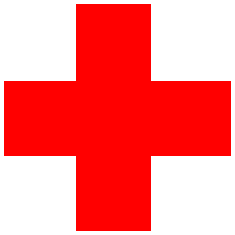
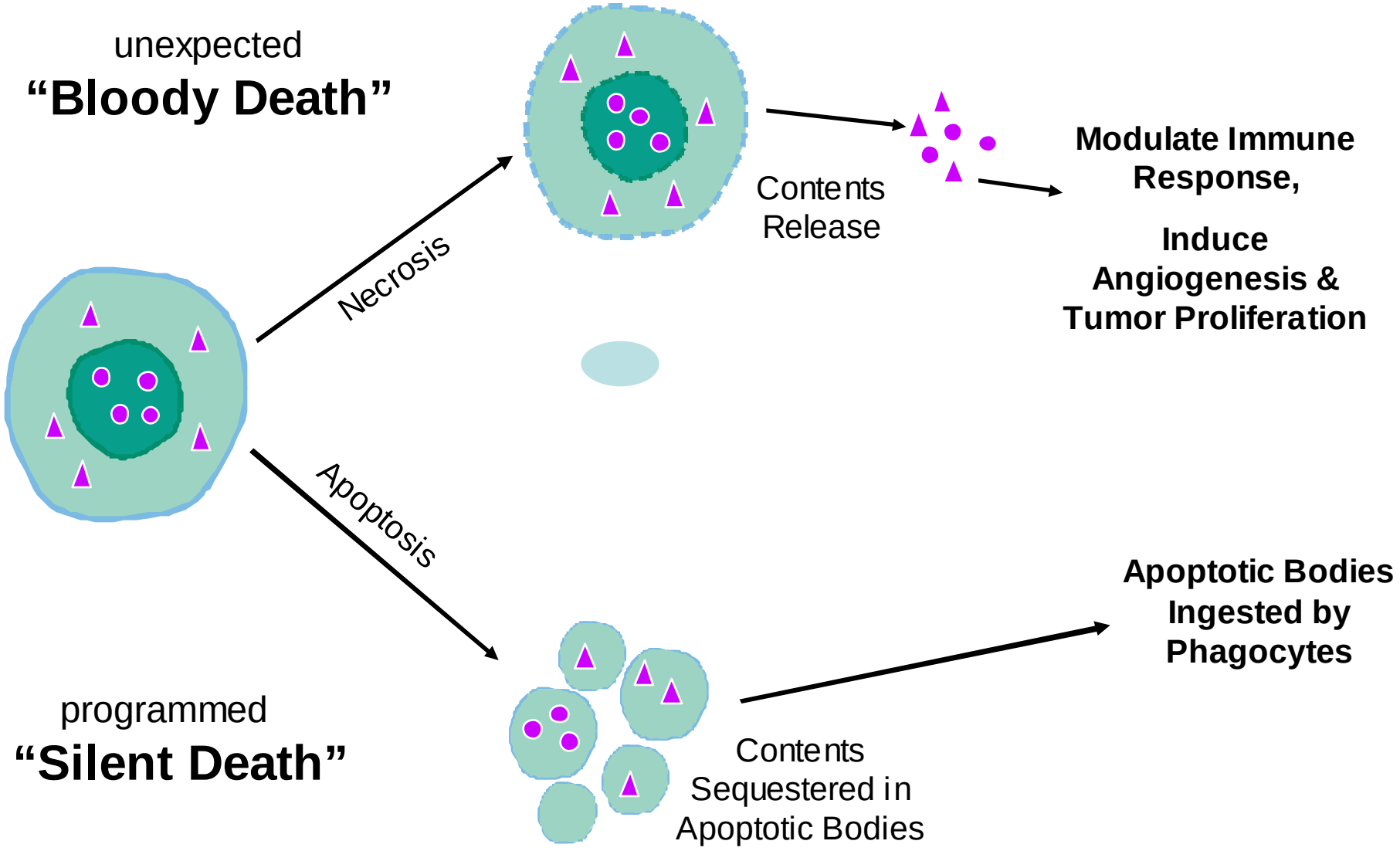


University of Pittsburgh, Hillmann Cancer Center, USA

Mode of Cell Death is Important for Danger Recognition



Damage-associated Molecular Patterns (DAMPs):

Cell Constituents:	HMGB1
	Heat shock proteins
	Uric Acid, ATP, Adenosine
	s100 proteins
	Hepatoma derived growth factor
	?Cardiolipin
Secreted molecules:	Fibrinogen domain A
	Surfactant protein A
Matrix elements:	Heparan sulfate
	Soluble hyluranan
	Fibronectin

Eos are Attracted By Cell Debris And Found In Necrotic Tissues

Stenfeldt AL, Wenneras C. (Immunology 2004)

In vitro

Cormier SA, Lee NA (J Leuk Biol, 2006)

In vivo

Eosinophils

- Asthma/autoimmune/allergic diseases
- Helminth infections

- Cancer (colorectal cancer patients with eosinophilia have a better prognosis)
  Lotfi et al., J Immunother. 2007

- Highly cytotoxic granules (MBP, EPO)
- Highest oxid. Burst compared to other leukocytes

Summary of background information and hypotheses

- Tumors undergo necrosis
  => release of DAMPs
- DAMPs influence tumor microenvironment

- Eos are attracted by DAMPs

Interaction between Eos & DAMPs ??

Experimental design:

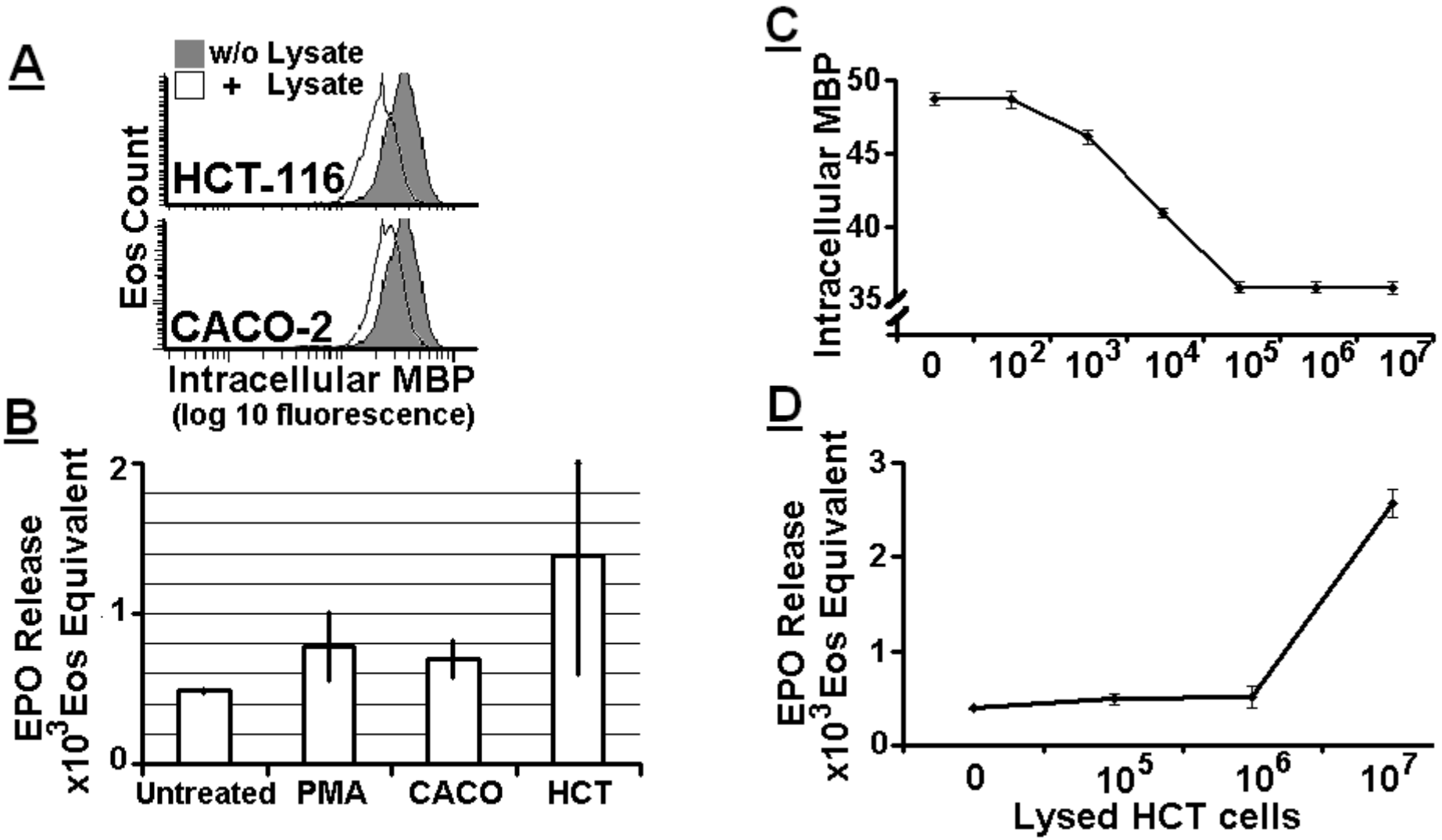
Induction of necrosis by repeated freeze/thaw cycles to obtain DAMPs

Stimulated Eos with DAMPs

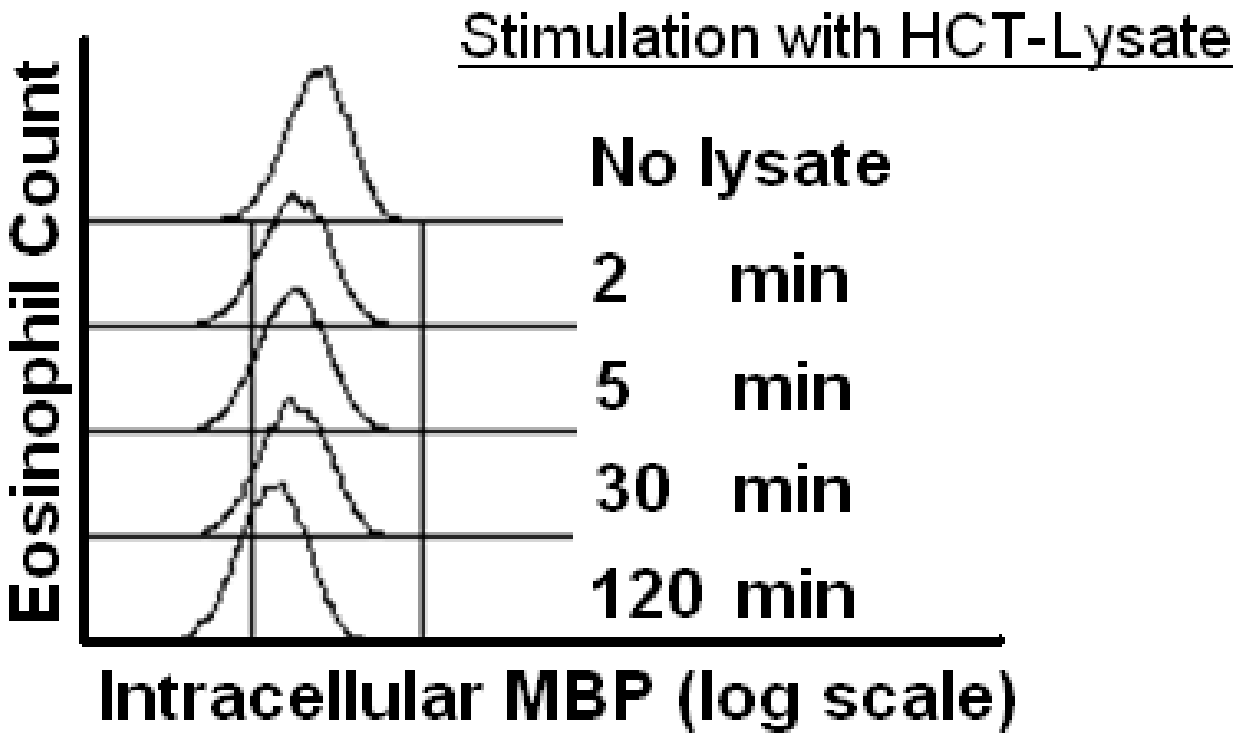
Read-Out:

- Degranulation (Release of MBP&EPO)
- Oxidative Burst (Generation of ROS)

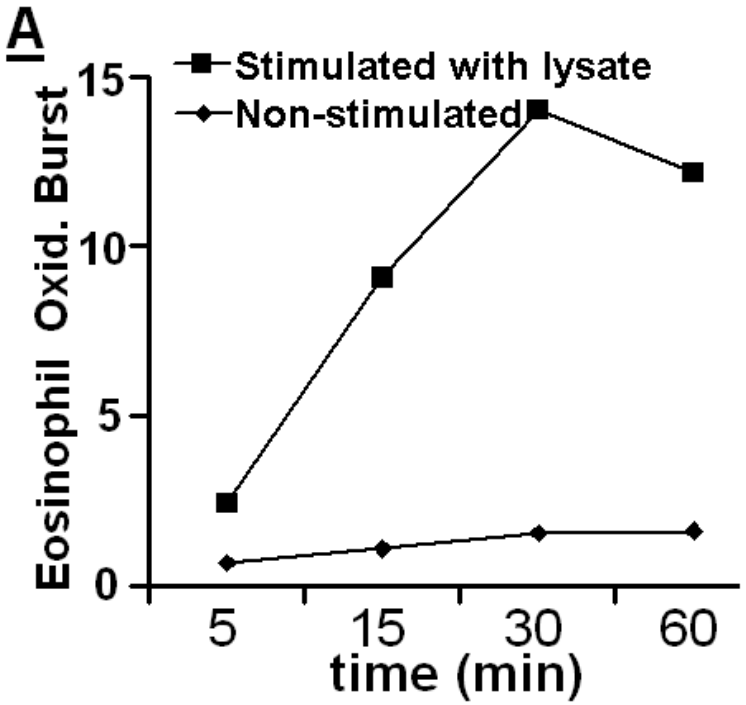
Necrotic Material induce Eos Degranulation

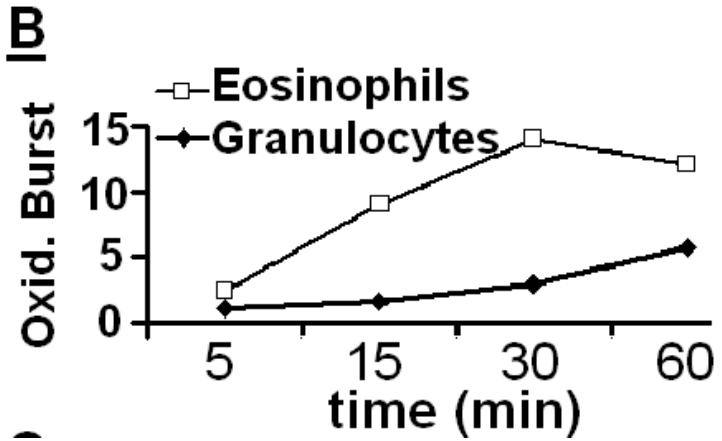


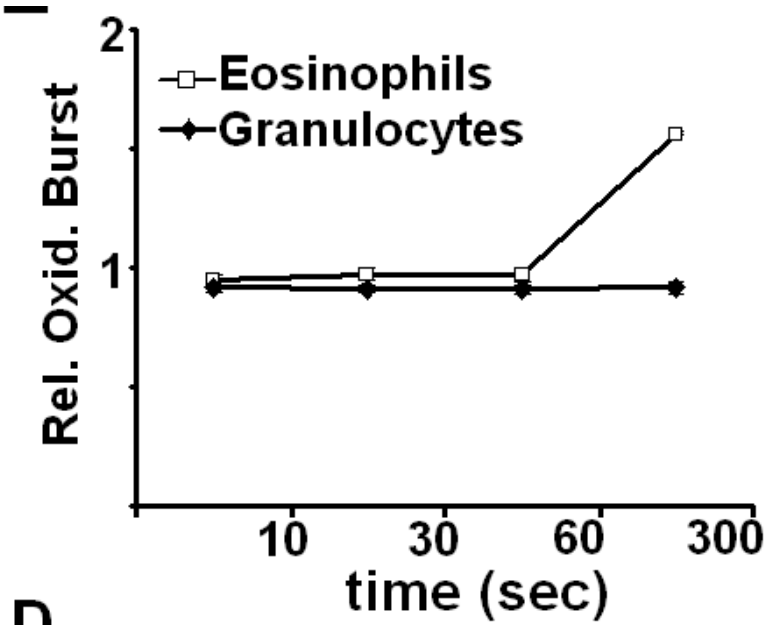
Necrotic Material induce Eos Degranulation

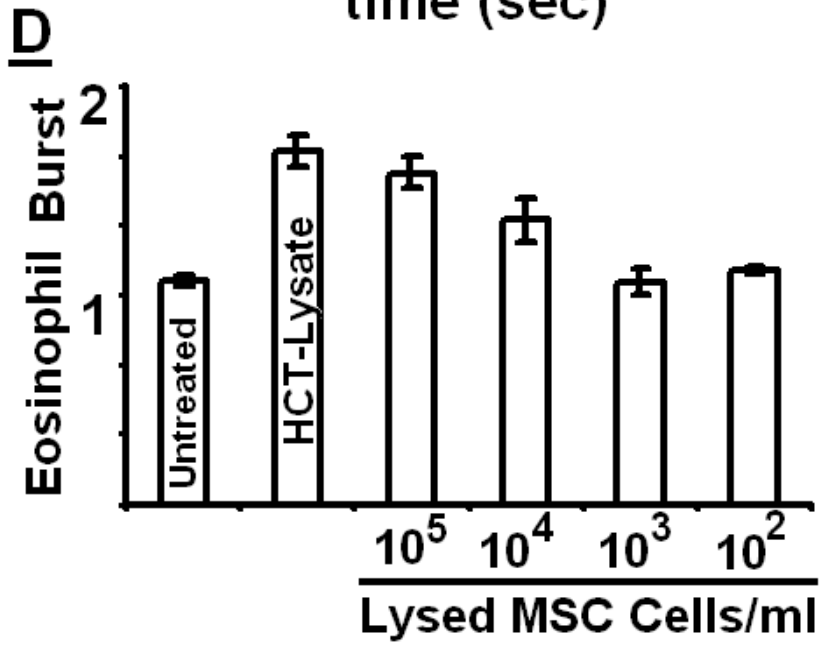


Necrotic Material Enhance Eos Oxid. Burst

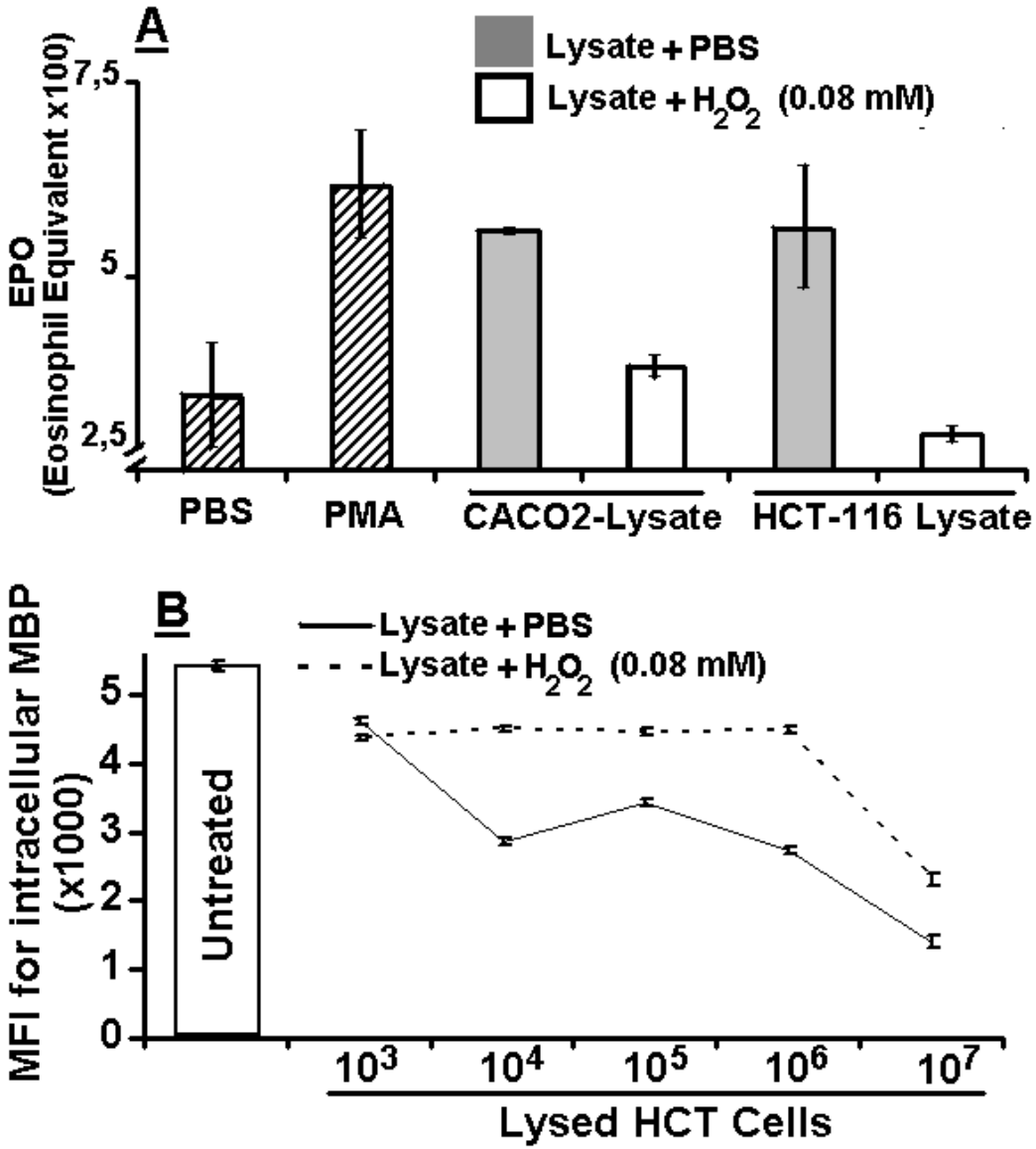




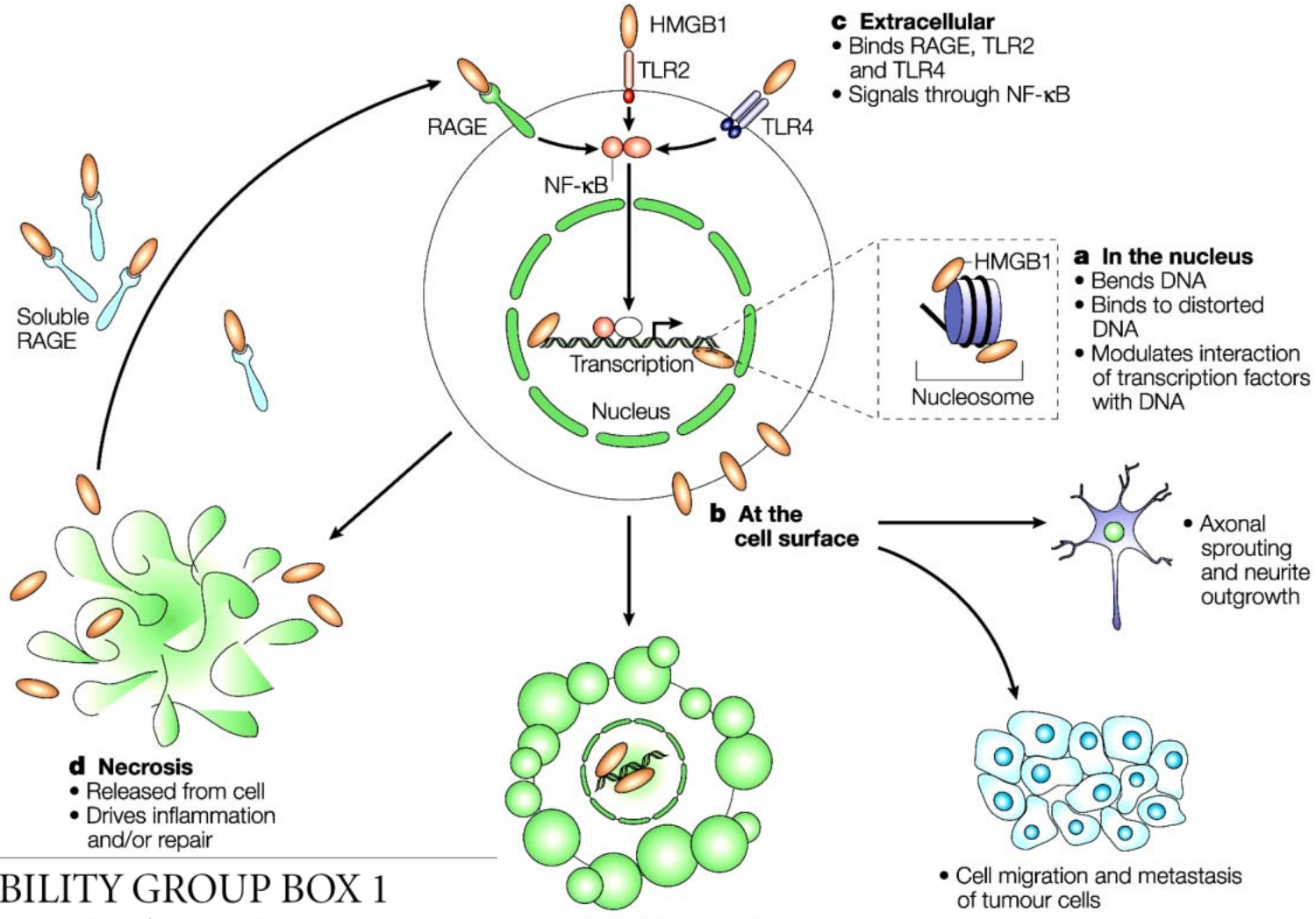




H2O2 Neutralizes The Effect Of Necrotic Material On Eosinophils.



Biology of HMGB1

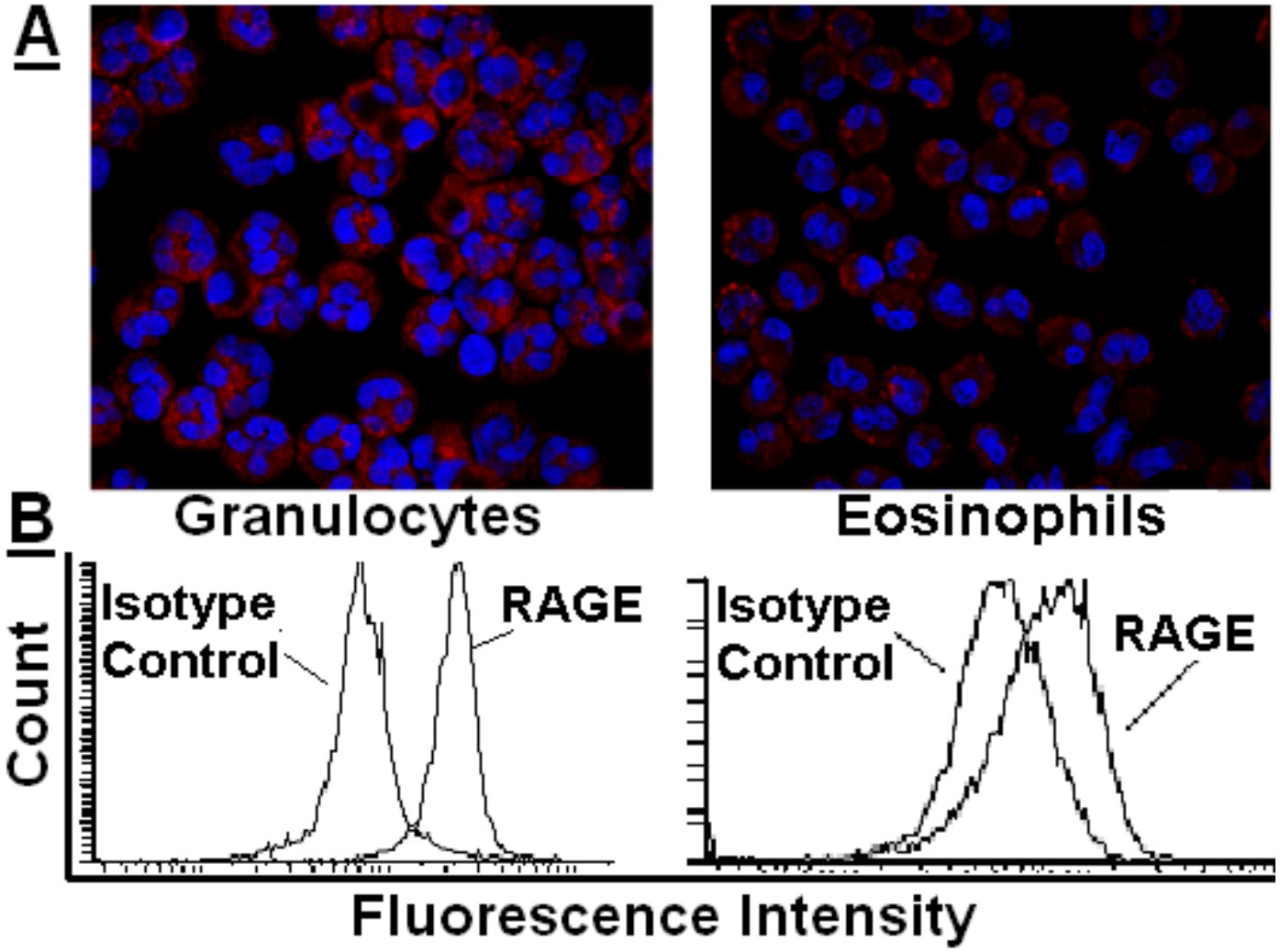


HIGH-MOBILITY GROUP BOX 1 PROTEIN (HMGB1): NUCLEAR WEAPON IN THE IMMUNE ARSENAL

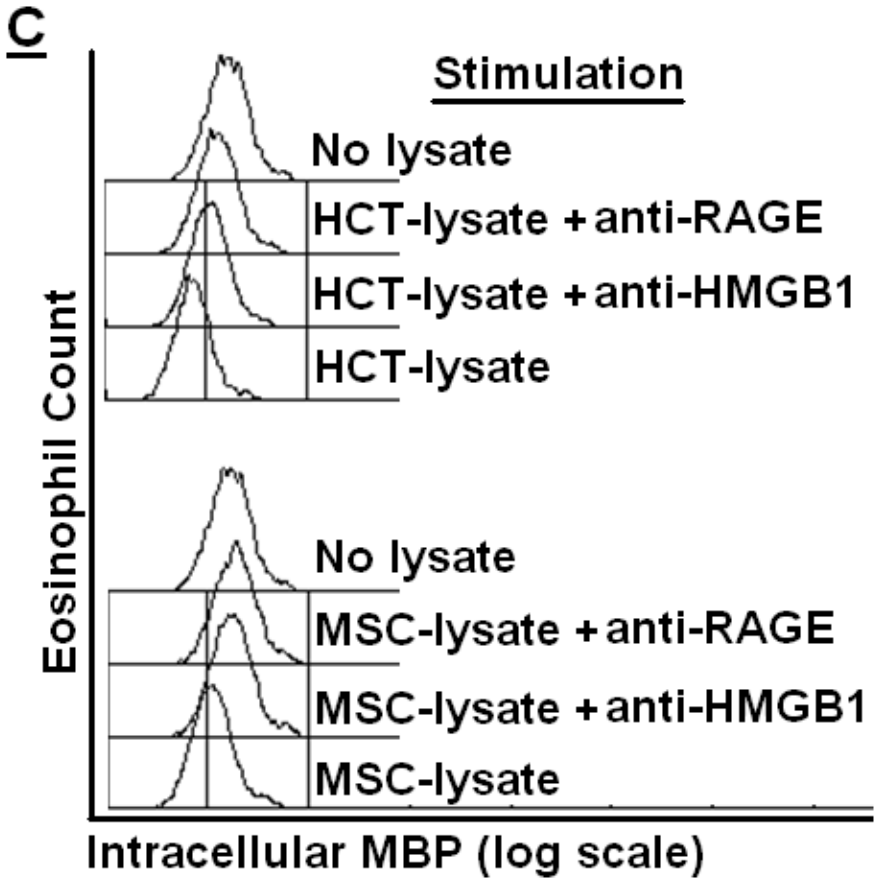
*Michael T. Lotze and ‡Kevin J. Tracey

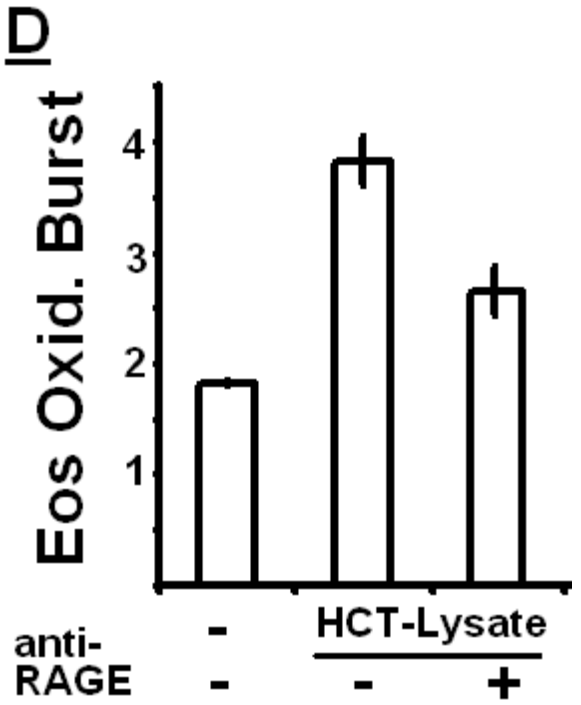
Nature Reviews | Immunology April 2005

The Receptor For Advanced Glycation End Products, RAGE on Eosinophils.

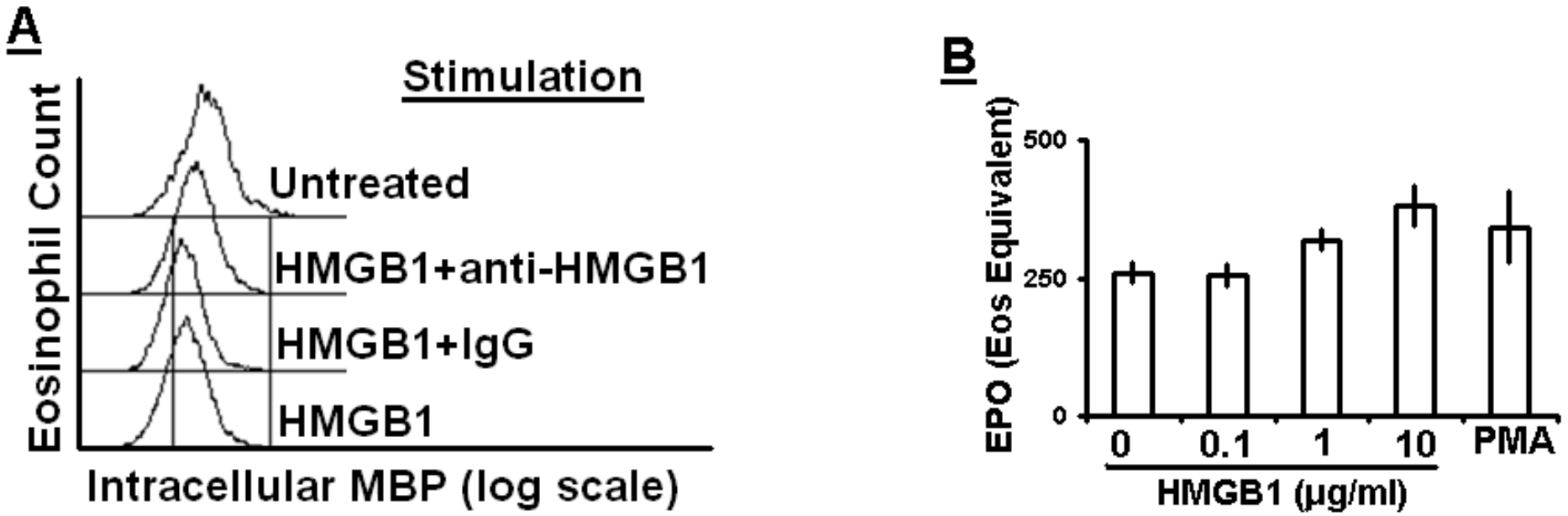


RAGE Participates in DAMPs-Induced Eosinophil Activation

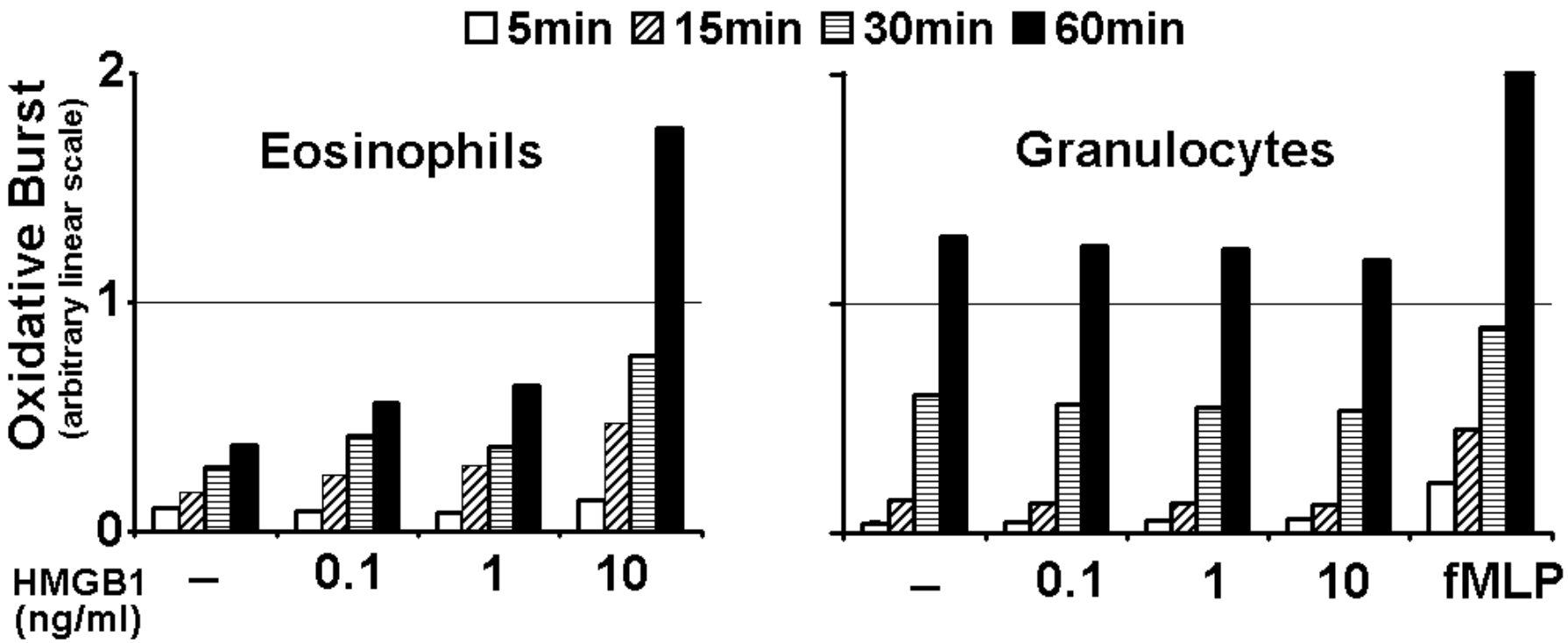




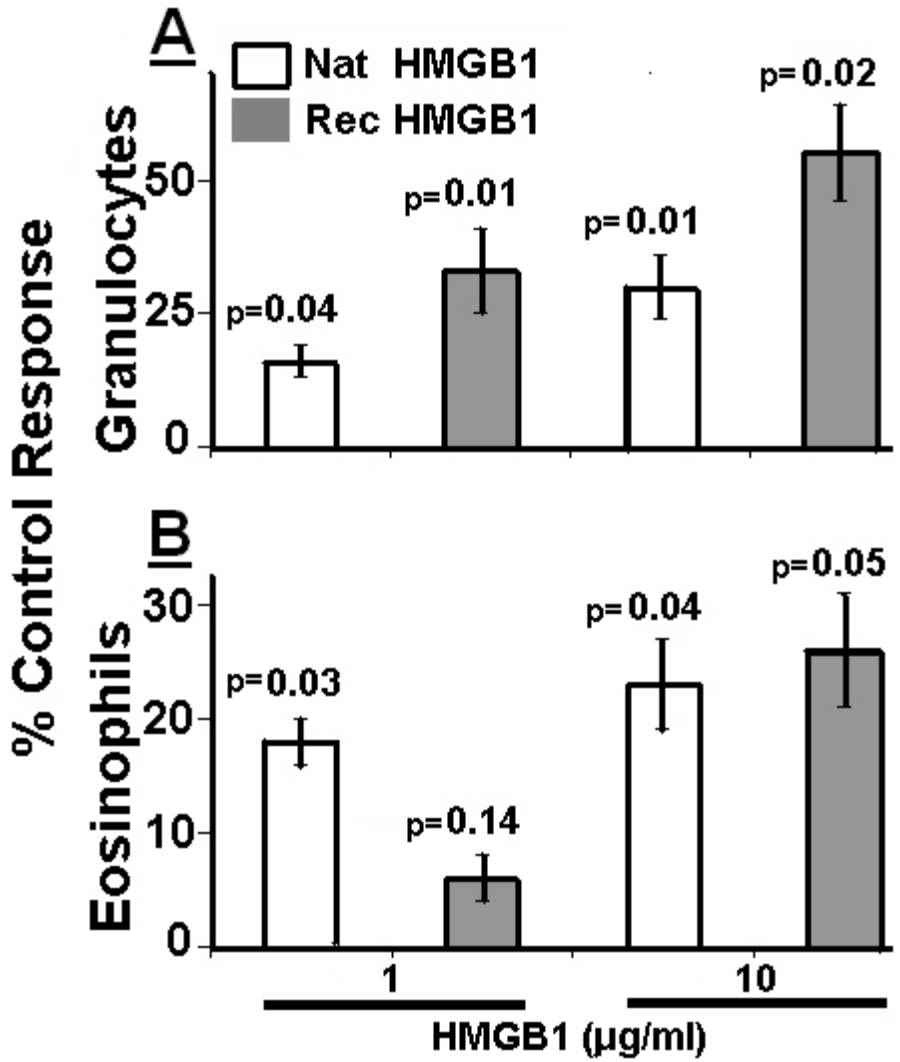
Human Eosinophils Degranulate Following HMGB1 Treatment



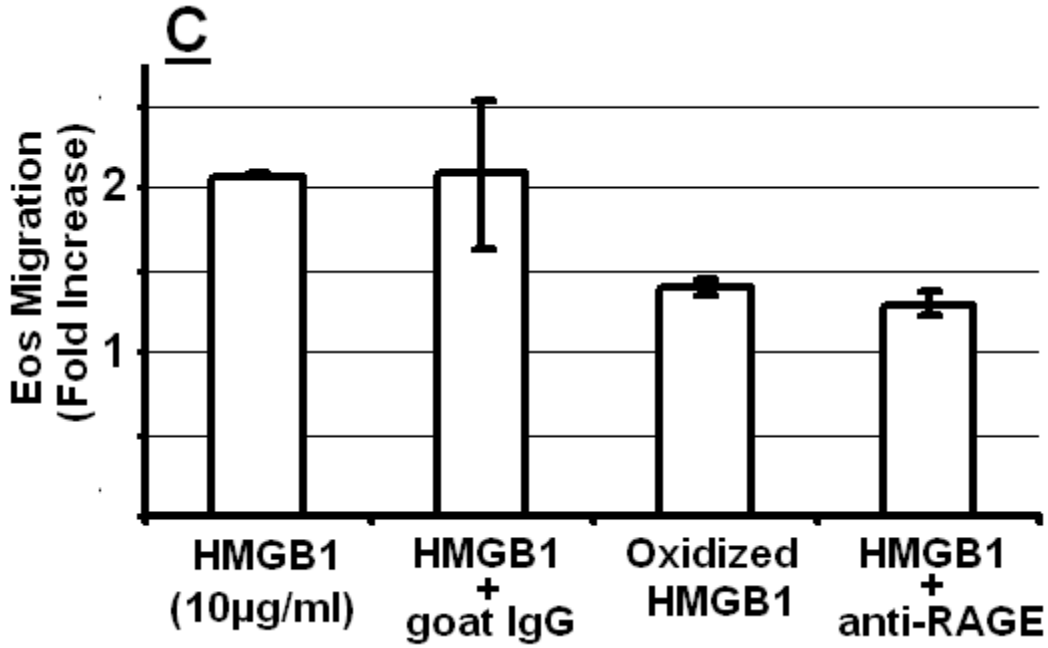
HMGB1 Specifically Enhances the Oxid. Burst of Eos When Compared With Neutros



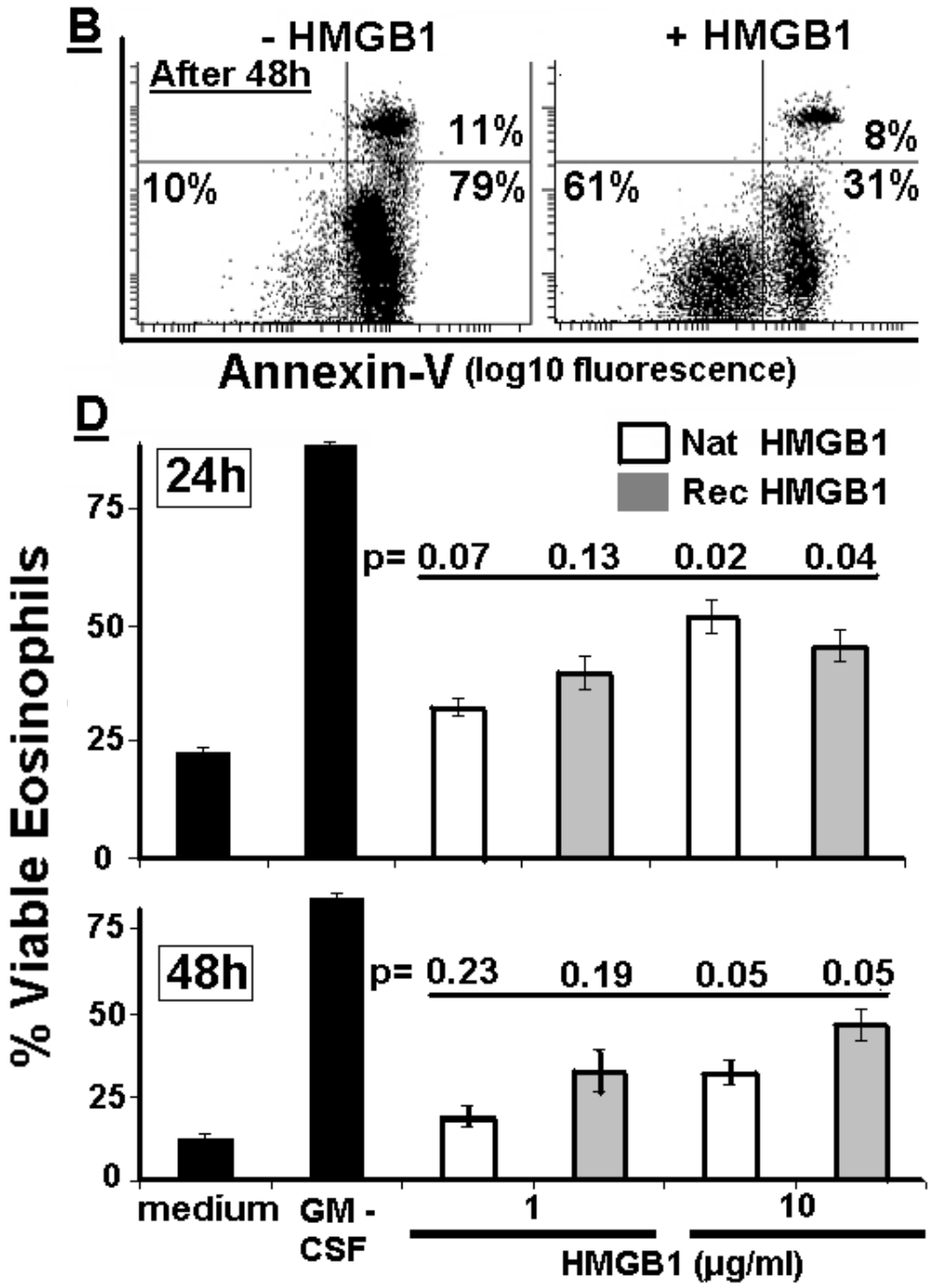
HMGB1 Serves As Chemoattractants For Human Granulos And Eos



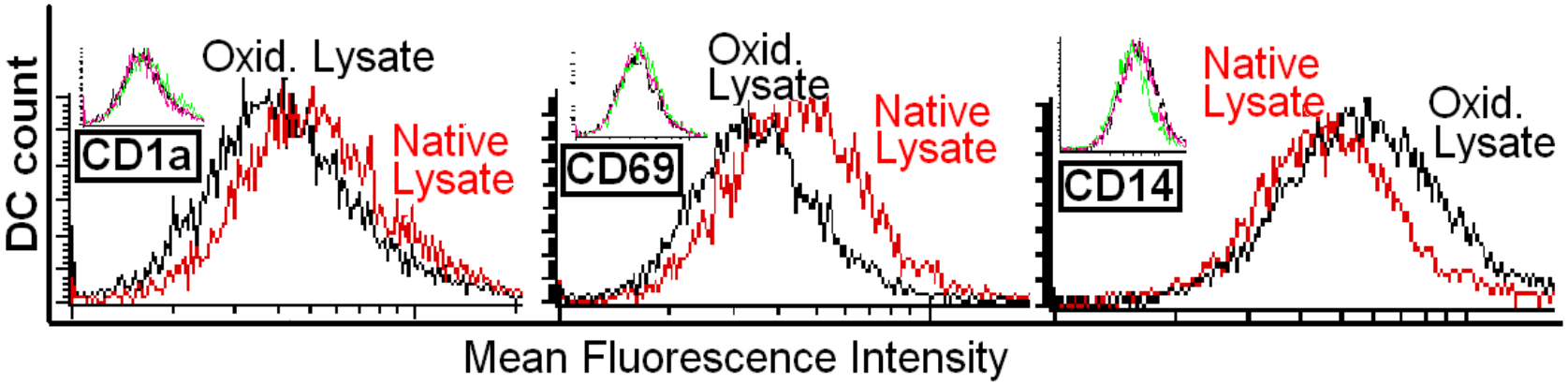
Inhibition of HMGB1 Induced Eos Migration



HMGB1 Enhance Survival Of Human Eosinophils



Oxidized DAMPs Lose Their Capapcity to Stimulate DCs

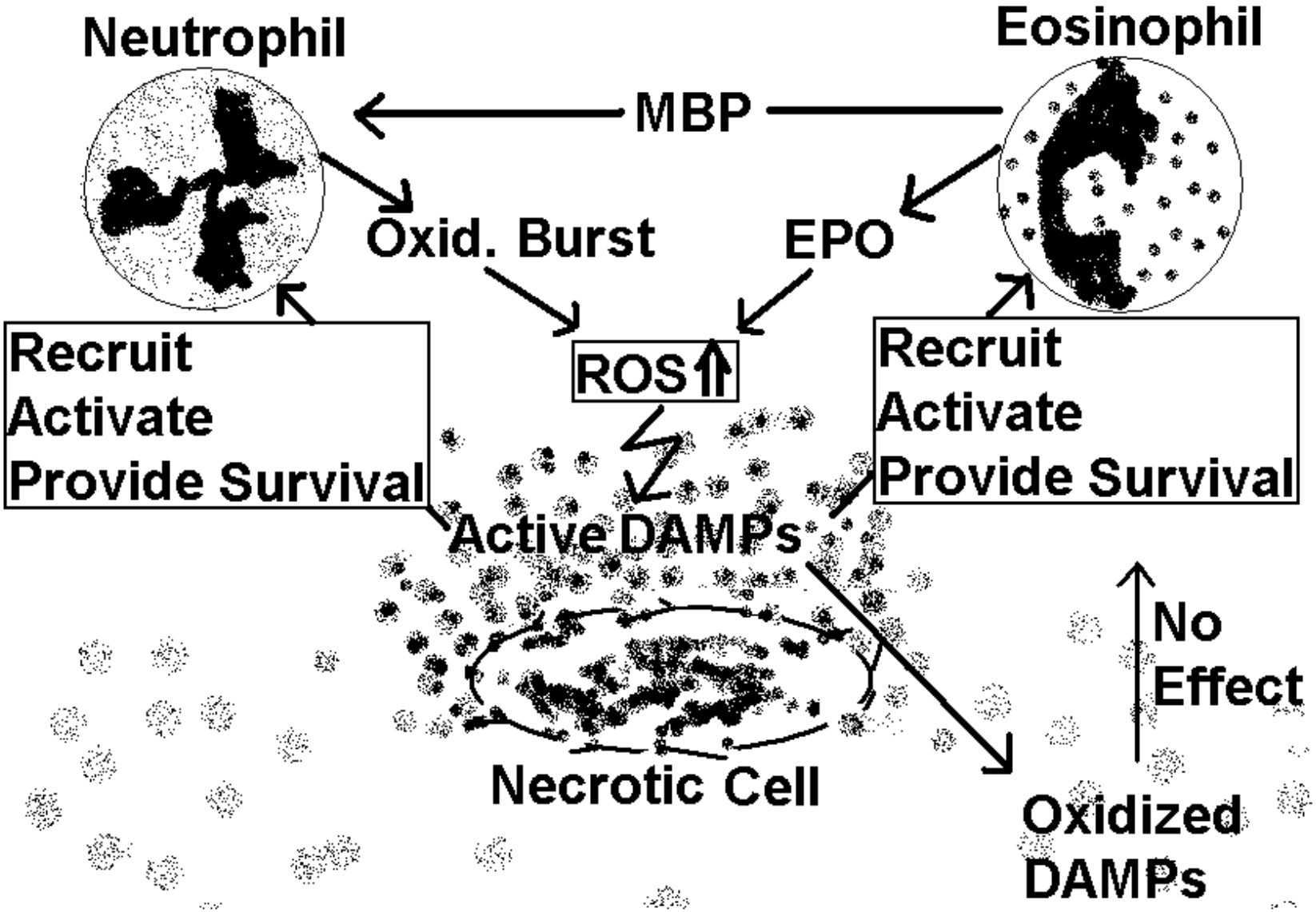


Marker of differentiation

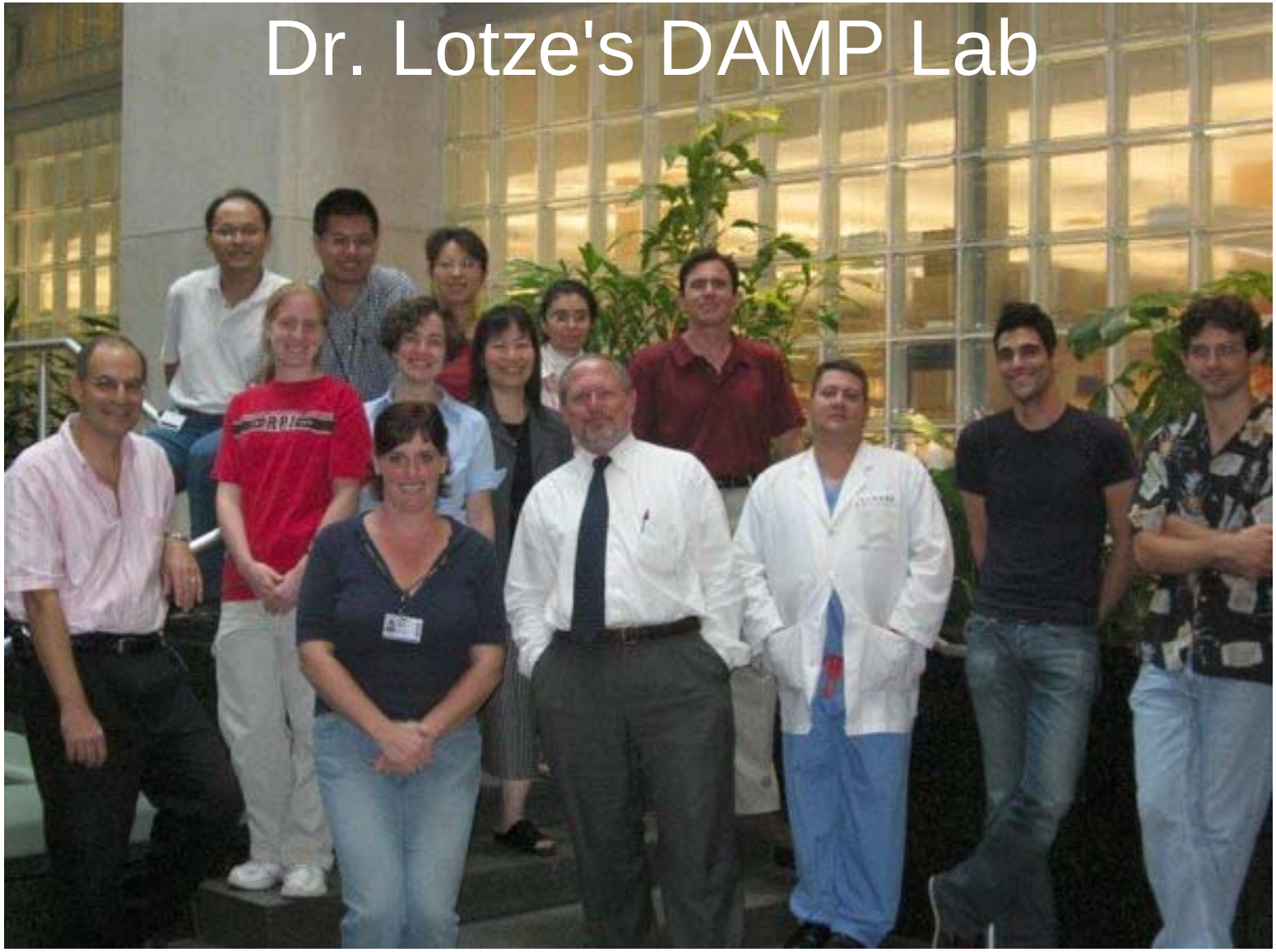
Aktivierungs-marker

Differenzierungs-marker

Eosinophils Promote Oxidation of DAMPs



Dr. Lotze's DAMP Lab



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Lotfi et al., J Immunol., Oct 1, 2009