

# Novel Therapies for Eosinophilic Disorders

Bruce S. Bochner, M.D.  
Cosner Scholar in Translational Research  
Professor of Medicine and Director  
Division of Allergy and Clinical Immunology  
Johns Hopkins Asthma and Allergy Center  
Baltimore, Maryland

## Disclosures

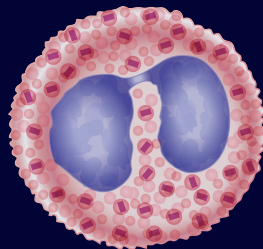
During the course of these NIH-funded studies, Dr. Bochner would have been entitled to a share of the University's potential royalties from the sales of products described in this presentation, as stipulated under a licensing agreement between GSK and the Johns Hopkins University.

Dr. Bochner has not received royalty payments because there have been no sales of products. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

## When you want to get rid of eosinophils there are many ways to do this

- Inhibit hematopoiesis
- Inhibit adhesion
- Inhibit migration
- Inhibit survival signals
- Actively induce apoptosis

## Examples of newer therapies selectively targeting eosinophils



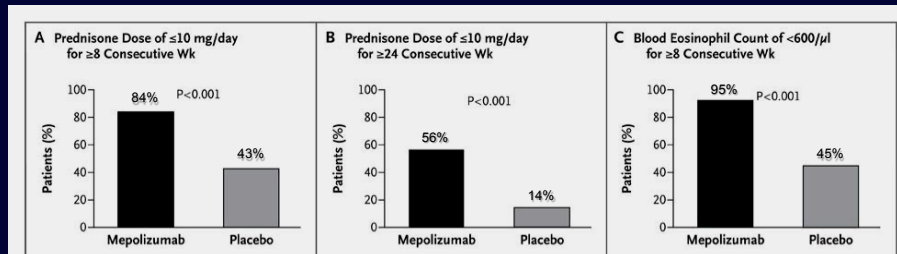
Anti-IL-5 and IL-5R  
(mepolizumab,  
reslizumab, benralizumab);  
imatinib mesylate;  
Siglec-8

# IL-5 as a therapeutic target in asthma

IL-5 is critical for

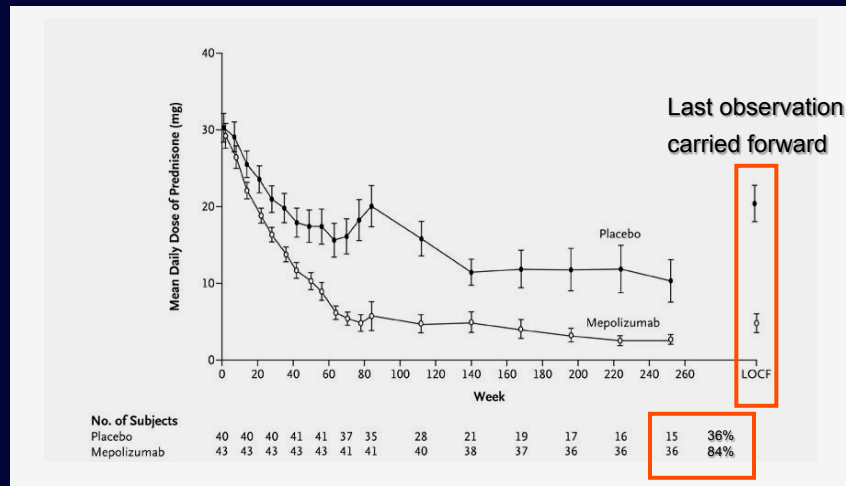
- Eosinophil maturation
- Eosinophil activation
- Eosinophil survival

## Efficacy of Mepolizumab Treatment in HES



Rothenberg ME et al. N Engl J Med 2008;358:1215-1228

## Efficacy of Mepolizumab Treatment in HES



Rothenberg ME et al. N Engl J Med 2008;358:1215-1228

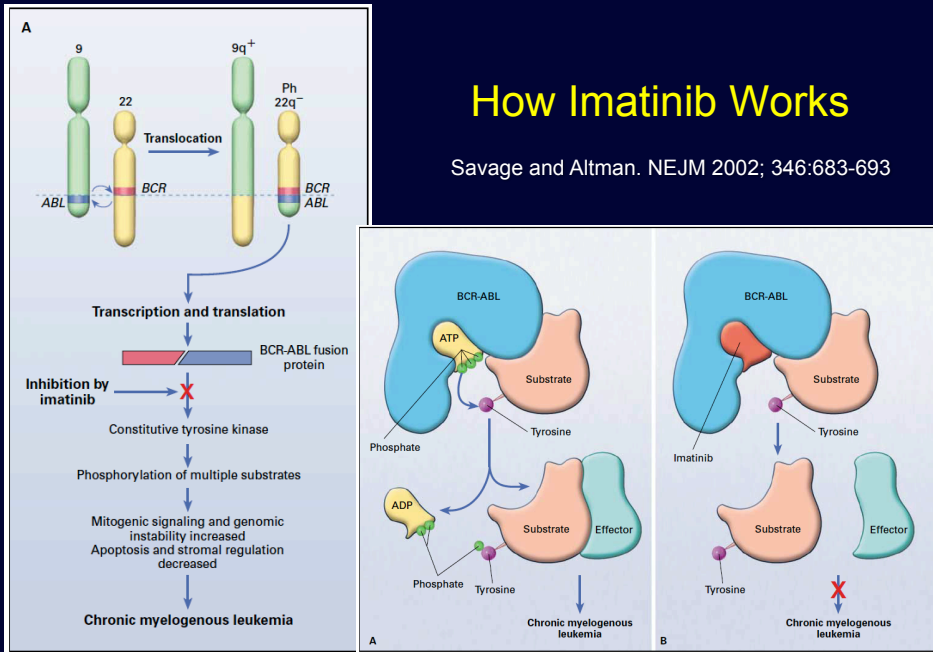
## Imatinib Mesylate (Gleevec®)

- Imatinib Mesylate (Gleevec®) is an inhibitor of the abnormal BCR-ABL tyrosine kinase found in chronic myelogenous leukemia.
- Gleevec® has been used to treat CML with great success.

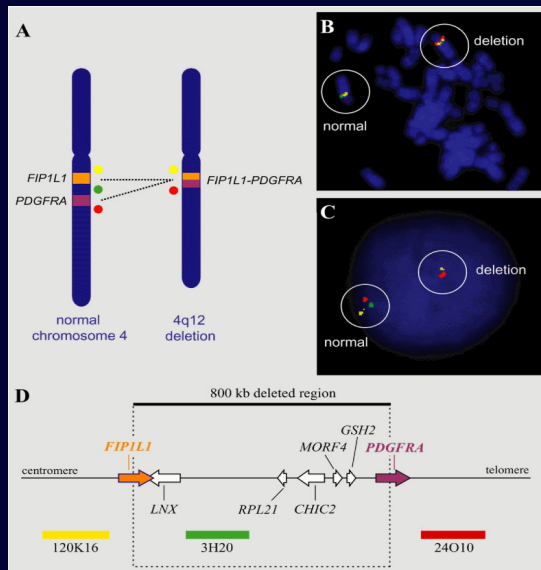
Savage and Altman. NEJM 2002; 346:683-693

## How Imatinib Works

Savage and Altman. NEJM 2002; 346:683-693



## FIP1L1/PDGFR4 deletion mutation in HES

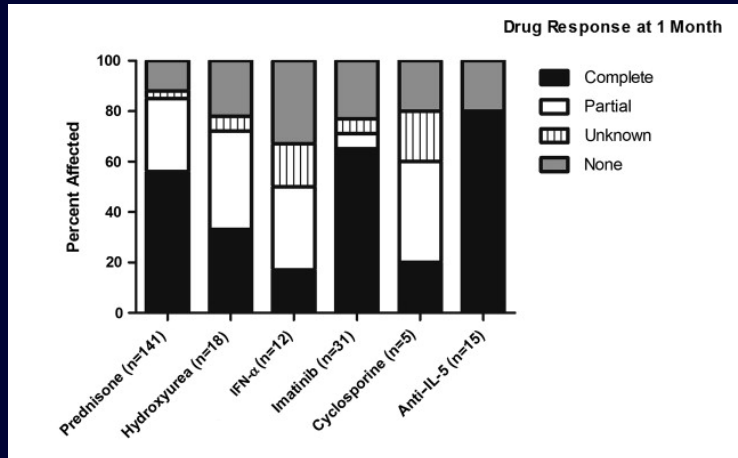


Occurred in 9 of 16 patients  
(56 percent;  
for some reason, all males)

FISH (Quest test #99895)  
PCR (Quest test 16099)

Cools et al. NEJM 348:1201, 2003 and Curr Opin Hematol 11:51, 2004

## HES - Multicenter Study Subjects: Initial Treatment Response



Ogogogu et al., J Allergy Clin Immunol 124:1319, 2009

## Does targeting eosinophils have a clinical benefit? Three studies in eosinophilic asthma that say “YES”

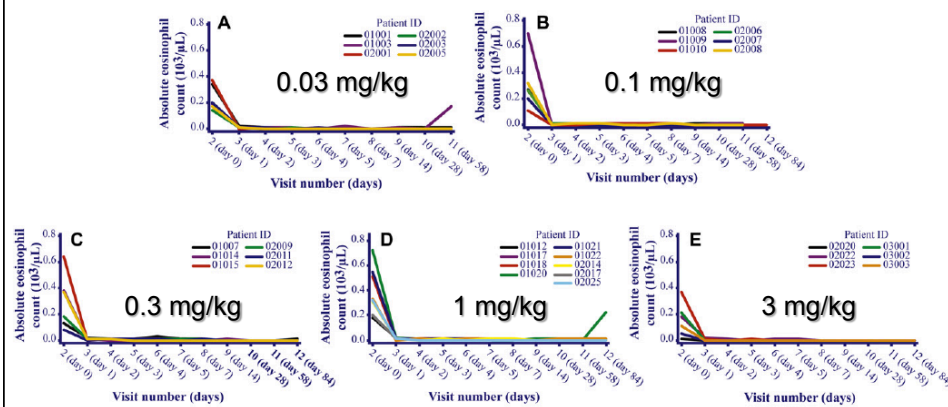
Paper	Drug	Lung eos	Exacerbations	FEV-1
Haldar/NEJM 2009	Mepolizumab 750 mg IV/ month	↓	↓	No change
Nair/NEJM 2009	Mepolizumab 750 mg IV/ month	↓	↓	Improved
Castro/Am J Respir Crit Care Med 2011 [Epub]	Reslizumab 3 mg/kg SQ/ month	↓	↓	Improved

## Does targeting eosinophils have a clinical benefit? Two studies in eosinophilic esophagitis that say “No”

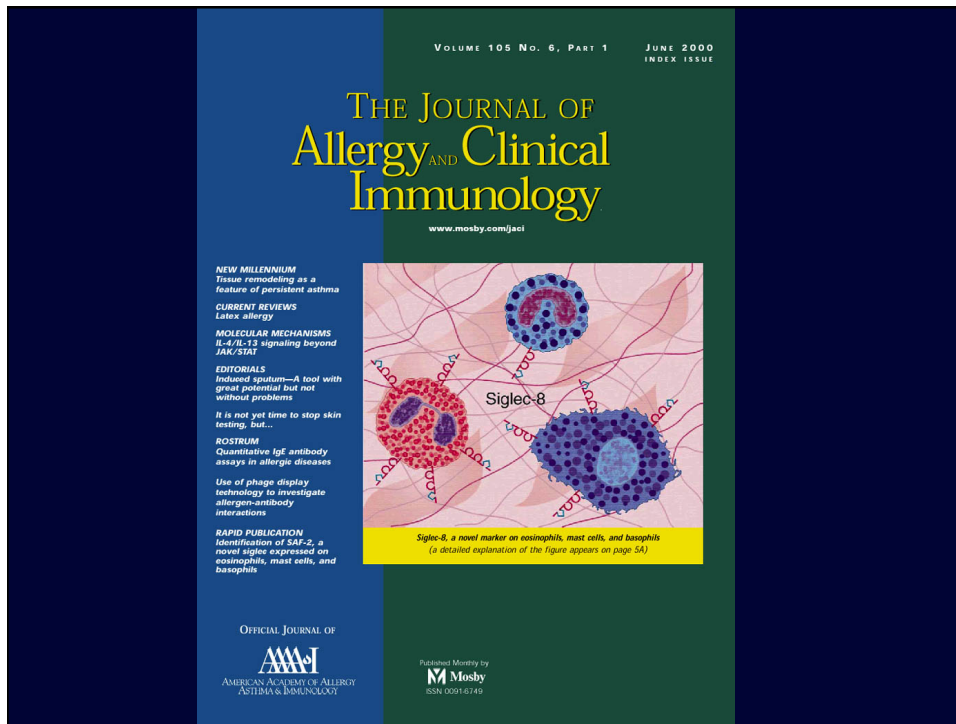
Paper	Drug	Esoph eos	Symptoms
Straumann/Gut 2010	Mepolizumab 750 mg IV/ month	↓*	No change
Spergel/IES abstract 2011	Reslizumab 1-3 mg/kg SQ/ month	↓	↓ BUT so did placebo!

\* Remodeling also improved

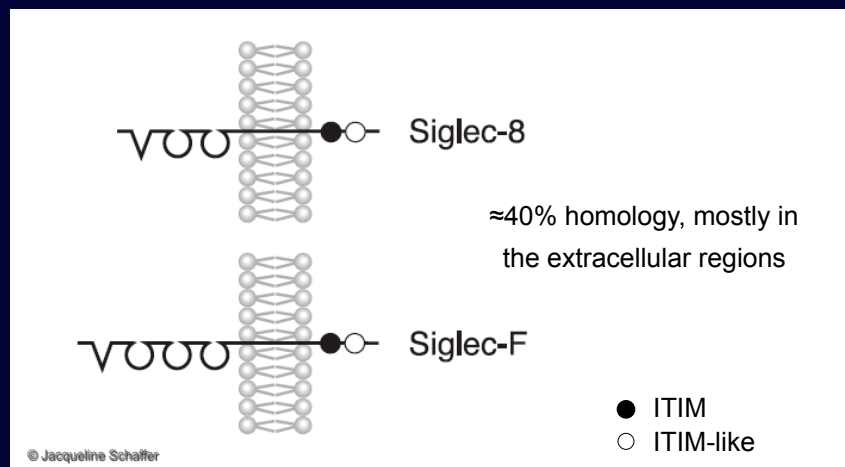
## Biological activity of MEDI-563 (benralizumab), an anti-IL-5 receptor $\alpha$ subunit mAb with ADCC activity



Busse et al., JACI 125: 1237, 2010



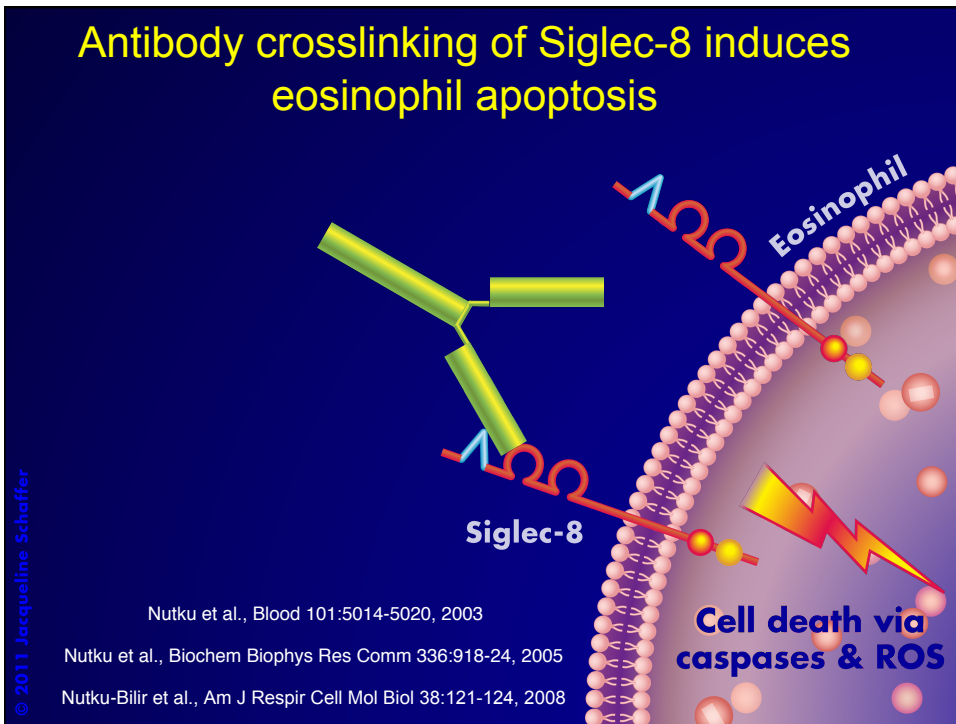
## Murine Siglec-F is the closest functional paralog to human Siglec-8



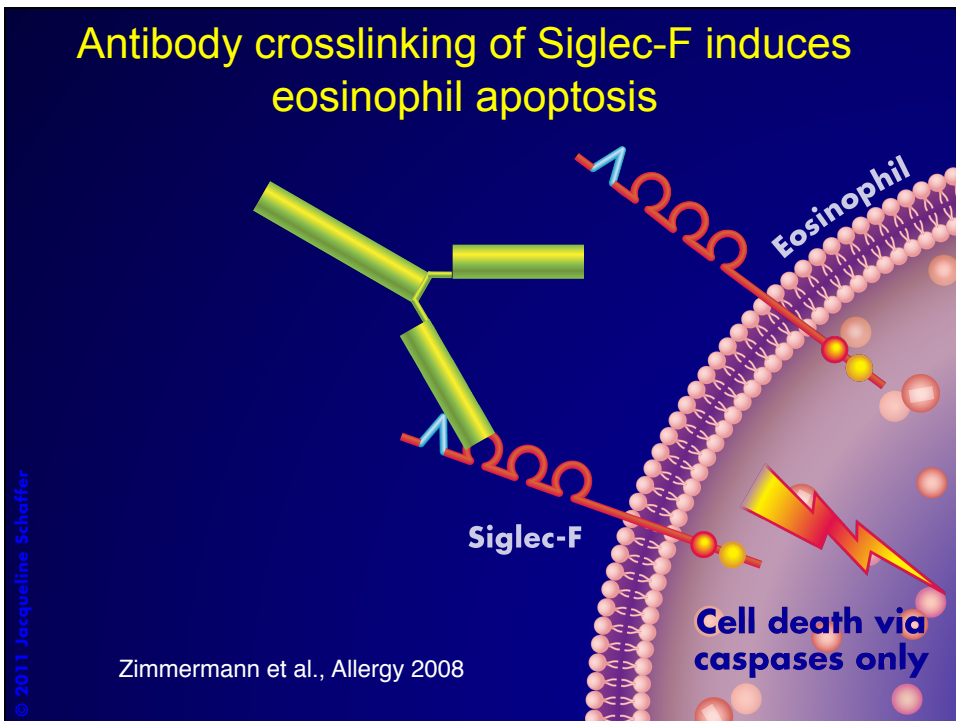
Modified from Bochner, Clin Exp Allergy 39:317, 2009



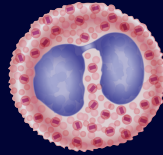
## Antibody crosslinking of Siglec-8 induces eosinophil apoptosis



## Antibody crosslinking of Siglec-F induces eosinophil apoptosis



## Proof of Concept in the mouse: *in vivo* effects of Siglec-F antibody



Decreased blood and tissue eosinophils;  
decreased GI and lung fibrosis

Zimmermann et al., Allergy 2008

Song et al., Clin Immunol 2009

Song et al., J Immunol 2009

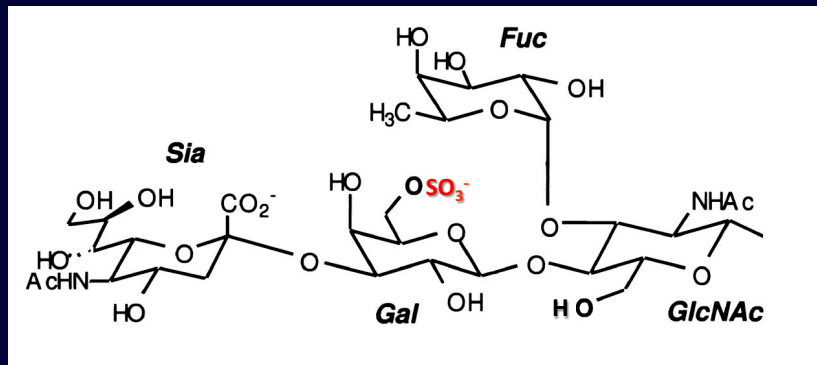
Rubinstein et al., J Pediatr Gastroenterol Nutr 2011

## Issues Regarding Testing of Siglec-8 mAb as Therapy

- Expressed on immature bone marrow cells?
  - NO
- Expressed on eosinophil and mast cell malignancies?
  - YES
- Preclinical animal model for testing?
  - Siglec-8 is not expressed below chimps

Hudson et al., J Clin Immunol 2011 DOI 10.1007/s10875-011-9589-4

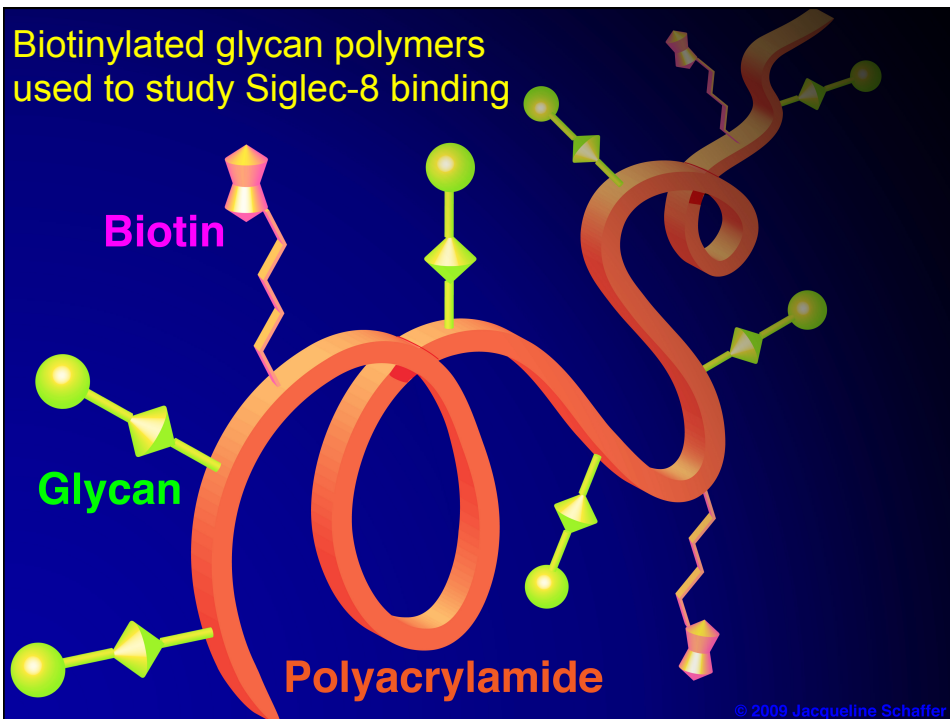
A candidate Siglec-8/-F ligand: the glycan  
6'-sulfated Sialyl Lewis X (6'-su-sLe<sup>x</sup>)



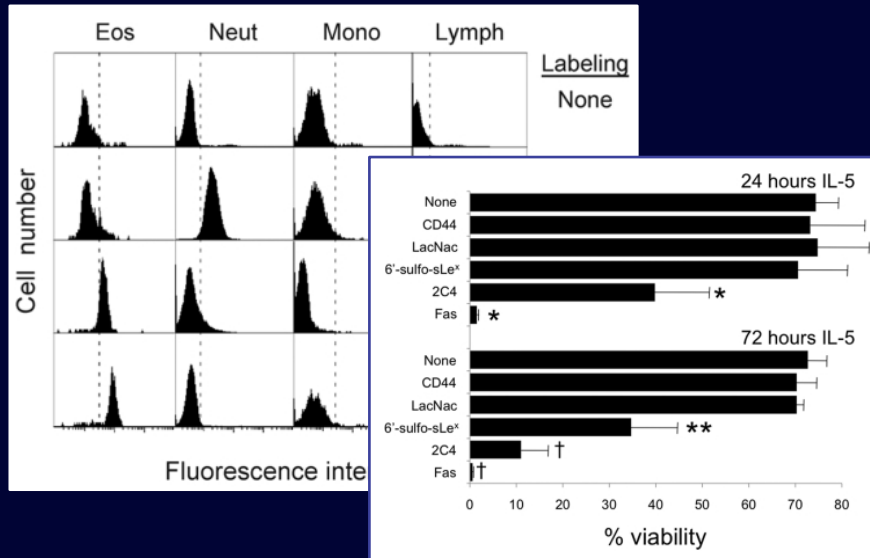
Bochner et al., J Biol Chem 280:4307, 2005

Tateno et al., Glycobiology 15:1125, 2005

Biotinylated glycan polymers  
used to study Siglec-8 binding



## Anti-Siglec-8 antibody & 6'Su-sialyl-Le<sup>x</sup> polymer bind to and kill activated human eosinophils



Hudson et al., J Pharm Exp Therap 330:608-612, 2009

## Anti-eosinophil treatment for eosinophilic disorders

Remaining questions:

- Unmet needs and costs?
- Right patients?
- Right endpoints?
  - Steroid-sparing?
  - Disease modifying or remitting?
  - Disease preventing?