Novel Therapies for Eosinophilic Disorders

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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

Efficacy of Mepolizumab Treatment in HES


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

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**FIP1L1/PDGFRα 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)

HES - Multicenter Study Subjects: Initial Treatment Response

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

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

<table>
<thead>
<tr>
<th>Paper</th>
<th>Drug</th>
<th>Lung eos</th>
<th>Exacerbations</th>
<th>FEV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldar/NEJM 2009</td>
<td>Mepolizumab 750 mg IV/ month</td>
<td>↓</td>
<td>↓</td>
<td>No change</td>
</tr>
<tr>
<td>Nair/NEJM 2009</td>
<td>Mepolizumab 750 mg IV/ month</td>
<td>↓</td>
<td>↓</td>
<td>Improved</td>
</tr>
<tr>
<td>Castro/Am J Respir Crit Care Med 2011 [Epub]</td>
<td>Reslizumab 3 mg/kg SQ/ month</td>
<td>↓</td>
<td>↓</td>
<td>Improved</td>
</tr>
</tbody>
</table>
Does targeting eosinophils have a clinical benefit? Two studies in eosinophilic esophagitis that say “No”

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

* Remodeling also improved

Biological activity of MEDI-563 (benralizumab), an anti-IL-5 receptor α subunit mAb with ADCC activity

Busse et al., JACI 125: 1237, 2010
Murine Siglec-F is the closest functional paralog to human Siglec-8

~40% homology, mostly in the extracellular regions

Modified from Bochner, Clin Exp Allergy 39:317, 2009
Antibody crosslinking of Siglec-8 induces eosinophil apoptosis

Nutku et al., Blood 101:5014-5020, 2003
Nutku et al., Biochem Biophys Res Comm 336:918-24, 2005

Antibody crosslinking of Siglec-F induces eosinophil apoptosis

Zimmermann et al., Allergy 2008
Proof of Concept in the mouse: \textit{in vivo} effects of Siglec-F antibody

\begin{itemize}
  \item Decreased blood and tissue eosinophils; decreased GI and lung fibrosis
  \item Zimmermann et al., Allergy 2008
  \item Song et al., Clin Immunol 2009
  \item Song et al., J Immunol 2009
  \item Rubinstein et al., J Pediatr Gastroenterol Nutr 2011
\end{itemize}

Issues Regarding Testing of Siglec-8 mAb as Therapy

\begin{itemize}
  \item Expressed on immature bone marrow cells? 
    \begin{itemize}
      \item NO
    \end{itemize}
  \item Expressed on eosinophil and mast cell malignancies? 
    \begin{itemize}
      \item YES
    \end{itemize}
  \item Preclinical animal model for testing? 
    \begin{itemize}
      \item Siglec-8 is not expressed below chimps
    \end{itemize}
\end{itemize}

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\textsuperscript{x})

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

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Anti-Siglec-8 antibody & 6'Su-sialyl-Le$^x$ 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?