Blocking IL-17C reverses the disease signature in a mouse model of atopic dermatitis

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Disclosures

The authors are employees of Galapagos or Morphosys
**IL-17C & skin**

**Background**

- Meanwhile the role of IL-17C was well described in psoriasis
  - human lesional psoriatic skin
  - imiquimod-induced skin inflammation model

**Hypothesis:** could IL-17C play also a role in other skin inflammatory diseases by acting as an amplifier of local inflammation?

**Objective:** evaluate the role of MOR106, an anti-mouse/human IL-17C antibody, in atopic dermatitis (AD) mouse models.

*Swamy et al, Nat Immunol, 2011*
### MOR106: *h* IgG1

*In vitro* pharmacology profile

<table>
<thead>
<tr>
<th>Assay Type</th>
<th>Human IL-17C (pM)</th>
<th>Mouse IL-17C (pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Binding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selectivity across IL-17 family</td>
<td>No significant binding to other IL-17 family members (IL-17A, IL-17F, IL17D...)</td>
<td>19</td>
</tr>
<tr>
<td>SET apparent affinity (IgG/EC$_{50}$)</td>
<td>19</td>
<td>387</td>
</tr>
<tr>
<td><strong>Functional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receptor inhibition assay (IgG/IC$_{50}$)</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>NF-κB reporter assay (IgG/IC$_{50}$)</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Keratinocyte assay (IgG/IC$_{50}$)</td>
<td>319</td>
<td>112</td>
</tr>
</tbody>
</table>
Mouse AD model

Daily application of calcipotriol in EtOH (2 nmol on each ear)

Groups (N=8) | Treatment
--- | ---
Sham | isotype control Ab (10 mg/kg)
Calcipotriol | isotype control Ab (10 mg/kg)
Calcipotriol + MOR106 | MOR106 (10 mg/kg)
Calcipotriol + Dexamethasone | Dexamethasone (5 mg/kg q.d. p.o. starting at day 1)

- Ear skin thickness (daily)
- *In vivo* imaging (at day 5) — Prosense 680 (cathepsin activity)
- Transcriptomic analysis on ears

Model adapted from Li et al., 2006
MOR106 *in vivo* activity

**Ear thickness**

- MOR106 reduces calcipotriol-induced skin inflammation in ears

**Cathepsin activity**

- MOR106 reduces calcipotriol-induced skin inflammation in ears
MOR106 in mouse AD
Global transcriptomics (PCA)

- Method
  - Mouse AD ears (n=5 per group)
  - Agilent Array

- MOR106 impacts calcipotriol-induced effects on a global transcriptome level
MOR106 in mouse AD
Top ranked disease modulated genes

- MOR106 partially reverses the calcipotriol effects
MOR106 in mouse AD
Relevance in model

- Strong negative correlation between calcipotriol and MOR106 effects

Pairwise correlation
Spearman, $R = -0.91; R^2 = 0.83$

Calcipotriol effect
Up

Down

MOR106 effect
Up

Down

Absolute log2(FC) > 1
FDR < 0.01
MOR106 in mouse AD
Functions/Pathways

Skin barrier/epithelial integrity

Defensins

IL-17 & IL-22 modulated genes

Innate general inflammation
Mast cells

Th1
Th2
Th2 related chemokines

up
down
• Many of the genes identified are relevant for
  ➢ human AD disease (assessed in six public transcriptomic studies)
Conclusion

• MOR106, a potent and selective human IgG1 monoclonal anti-IL-17C neutralising antibody:
  ➢ Strongly reduced the anti-inflammatory effects in the mouse calcipotriol-induced AD model
  ➢ Clearly affected AD-related gene expression signature

• Evaluation of MOR106 in Phase I with AD patients ongoing (NCT02739009)
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