GPR84, a novel target for the development of therapies for IBD

Sonia Dupont¹, Frédéric Labéguère¹, Roland Blanqué¹, Steve de Vos², Philippe Clément-Lacroix¹, Isabelle Parent¹, Corinne Saccomani¹, Luc Nelles², Annick Hagers², Céline Cottereaux¹, Didier Merciris¹, Marie-Christine Ceccotti¹, Cécile Belleville Da Costa¹, Stephen Fletcher, Reginald Brys²

¹GALAPAGOS, Romainville, France,
²GALAPAGOS, Mechelen, Belgium

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- Disclosures
  - All authors are employees of Galapagos
GPR84 for IBD therapy

- Compelling evidence: GPR84 as a target in IBD
- GLPG1205, a clinical candidate active in IBD model
GPR84
Novel target in inflammation

- Class A GPCR, Gi coupled
- Ligands: MCFA (9-14 carbon chain length), DIM, Embelin, 6-OAU
- Limited knowledge on biological role:
  - **T cell**: increased IL4 production in activated KO cells (Venkataraman et al., 2005)
  - **Macrophage**: MCFA potentiate LPS-induced IL12 secretion (Wang et al., 2006)
  - **Neutrophil & macrophage**: 6-OAU induces chemotaxis and accumulation of PMNs & macrophages in air pouch model (Suzuki et al., 2013)
  - Expression strongly increased in RASFs upon cytokine treatment & in paws of animals subjected to CIA (GLPG own data)

Early data suggest a potential role in inflammation for GPR84
## Role in IBD

### Expression in relevant cell types/tissues

<table>
<thead>
<tr>
<th>Cell type / tissue</th>
<th>Basal expression</th>
<th>Induced expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human dendritic cells</td>
<td>No</td>
<td>5-30 -fold by LPS</td>
</tr>
<tr>
<td>Human/rat neutrophils</td>
<td>Medium *</td>
<td>3 -fold by LPS</td>
</tr>
<tr>
<td>Human macrophages</td>
<td>Low *</td>
<td>3-10 -fold by LPS</td>
</tr>
<tr>
<td>Human T-cells</td>
<td>Medium</td>
<td>No induction by LPS</td>
</tr>
<tr>
<td>Human intestinal epithelial cells (differentiated Caco-2)</td>
<td>No</td>
<td>No induction by LPS</td>
</tr>
<tr>
<td>Human whole blood</td>
<td>Medium</td>
<td>~10-fold by LPS</td>
</tr>
<tr>
<td>Mouse colon</td>
<td>Low</td>
<td>Induced in DSS model</td>
</tr>
<tr>
<td>Human colon</td>
<td>Low</td>
<td>Under evaluation</td>
</tr>
</tbody>
</table>

- RT-qPCR data; *: induced by cell incubation; meta-analysis, *** p<0.001 Student t-test versus intact

**Expression in neutrophils and macrophages, not epithelial cells**  
**Strong induction in diseased conditions**
Role in IBD
Regulation of neutrophil chemotaxis

- Embelin- (but not IL-8-, C5a- and fMLP-) induced chemotaxis is blocked by GPR84 antagonists
- Rat macrophage chemotaxis: induced by GPR84 agonists, blocked by GPR84 antagonists (not shown)

GPR84 regulates biology of primary human cells involved in IBD pathogenesis
IBD model

Chronic mouse colitis model: setup

• Experimental design (Wirtz et al., 2007)
  ➢ BALB/c mouse,
  ➢ 3 cycles 5 days DSS 4% +2 days H2O

• Disease activity index (DAI)
  [from 0 to 12] composed of:
  ➢ weight loss [0-4]
  ➢ stool consistency [0-4]
  ➢ rectal bleeding [0-4]

• Histology score (Nishitani et al., 2009)

• Immunohistochemistry

* p<0.05, ** p<0.01, *** p<0.001 Student t-test versus intact
Efficacy in IBD

Efficacy of GLPG1205 in a chronic colitis model (1)

Mouse IBD model (DSS, chronic setting, po qd dosing)

GLPG1205 efficacy in mouse DSS model similar to cyclosporin and sulfasalazine

Minimal efficacy dose established at 3mg/kg po qd
Efficacy in IBD
Efficacy of GLPG1205 in a chronic colitis model (2)

**Histological analysis**
Mouse IBD model
(DSS, chronic setting, po qd dosing)

Significant efficacy in mouse DSS model, prevents colon lesion and neutrophil infiltration, effect similar to cyclosporin and sulfasalazine

- **Lesion score**
- **Neutrophil density**

*Meta analysis of 3 independent experiments*

** p<0.01, *** p<0.001 Tukey’s multi-comparison test versus Diseased*
GPR84 for IBD therapy
GLPG1205 ready to be tested in patients

- GPR84 inhibition prevents neutrophil and macrophage chemotaxis induced by specific triggers
- Medicinal chemistry delivered GPR84 antagonist GLPG1205
- First *in vivo* efficacy data ever with GPR84 inhibitor: GPR84 inhibition prevents disease progression in chronic mouse IBD model
- Phase 1 data on *poster P0341*: « Human safety, pharmacokinetics and pharmacodynamics of the GPR84 antagonist GLPG1205, a potential new approach to treat IBD »

GLPG1205 expected to enter Phase 2 patient studies in IBD

Slides available online on www.glpg.com