Blocking interleukin-15 as a new strategy for the treatment of Eosinophilic Esophagitis
Financial disclosure

- I am a co-founder, employee and shareholder of Calypso Biotech
IL-15: a pluripotent cytokine at the cross-road between innate and adaptive immunity in the GI tract

**Innate and Adaptive Immune Cell Homeostasis**

**Peripheral Immune Cell Function**

- Pro-inflammatory cytokine Production
- Stimulate Natural Killing
- Control lymphocyte trafficking
- T and B cell activation
IL-15 is involved in the pathogenesis of multiple GI immune diseases:

- Crohn’s disease
- Celiac disease
- ? Eosinophilic Esophagitis
IL-15 acts on multiple pathways relevant for EoE disease induction and maintenance

**Control of Th2 response**
- Amplifies IL-5 and IL-13 response in human cells (Mori 1996)
- Stimulates Th2 response in vivo in the mouse (Saikh 2008, Tang 2015, Mishra 2016)

**Control of relevant local immune cells**
- Amplification of IL-5 and IL-13 production in mouse MAIT cells (Holmvisk 2015)
- Homeostasis/activation of NKT cells that are important in EoE pathogenesis (Rayapudi 2014)
- Homeostasis and function of T_{REM} cells (de Gottardi 2016, Cheuk 2017)
- Development of ILC2 cells (Robinette 2017) that are enriched in EoE (Doherty 2015)

**Direct activity on eosinophils**
- Prevents apoptosis (Hoontrakoon 2002)

**Control of tissue response and microbiota**
- Activates esophageal epithelial cells (Zhu 2010)
- Master controller of tissue response in the gut (Jabri 2015)
- Promotes intestinal microbiota disbiosys (Meisel 2017)
IL-15 and IL-15Rα mRNA expression are part of the molecular signature of EoE.

Upregulated in EoE:
- CAPN14
- IL-15 & IL-15R
- IL-13

Downregulated in EoE:
- DSG1

Patients from Swiss EoE cohort (2012-2014)
IL-15 and IL-15Rα mRNA expression is elevated in the esophagus of active EoE patients, including corticoid non-responders.

Active: > 15 eos/hpf and clinical symptoms
IL-15 mRNA expression shows better correlation with an EoE molecular score than IL-13 mRNA expression.

EoE activity score based on subset of 25 most up- and down-regulated genes as published by Wen et al. (2013)
IL-15 protein is strongly expressed in esophageal epithelium from active EoE patients and co-stains T cells and eosinophils.
Intranasal antigen 3 x /week

Circulating levels of free IL-15 and IL-15/IL-15Rα complex increase in the mouse *Aspergillus fumigatus* model of EoE

**Aspergillus EoE mouse model**

Free IL-15

IL-15/IL-15Rα complex

An optimal anti-IL-15 antibody should block both *cis* and *trans* signaling

*From Y Jacques*
Anti-IL-15 but not anti-IL-13 antibody block esophageal eosinophilia in the mouse *Aspergillus fumigatus* model of EoE

Similar results reported in IL-15Rα KO mice (Zhu 2010) and IL-13 KO mice (Ninrajan 2013)
IL-15 as an immune checkpoint in EoE

Food antigens and inflammatory signals trigger IL-15 secretion by epithelial and immune cells.

IL-15 controls Th2 and iNKT cell responses, promotes epithelial inflammation, and prevents eosinophil apoptosis.

Th2 cells secrete cytokines that drive eosinophil recruitment and amplify the inflammatory and tissue response.
Conclusions

- There is a strong scientific and medical rationale to intercept IL-15 for the treatment of Eosinophilic Esophagitis:
  - IL-15 acts on multiple cells and pathways now recognized to be involved in EoE pathogenesis
  - IL-15 mRNA and protein expression are increased in active EoE
  - Blocking IL-15 is efficient in an experimental model of EoE
  - IL-15 expression correlates well with an EoE molecular disease activity score
  - IL-15 is well differentiated from other targets such as IL-13, as a broader and more upstream immune checkpoint

- Calypso Biotech develops CALY-002, a best-in-class anti-IL-15 antibody with unique neutralization of IL-15 cis and trans signaling, for the treatment of EoE and other severe gastro-intestinal disorders.
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