A Novel Human IL-22-Secreting Synthetic Biotic Medicine for the Treatment of Inflammatory Bowel Disease

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Digestive Disease Week (DDW)

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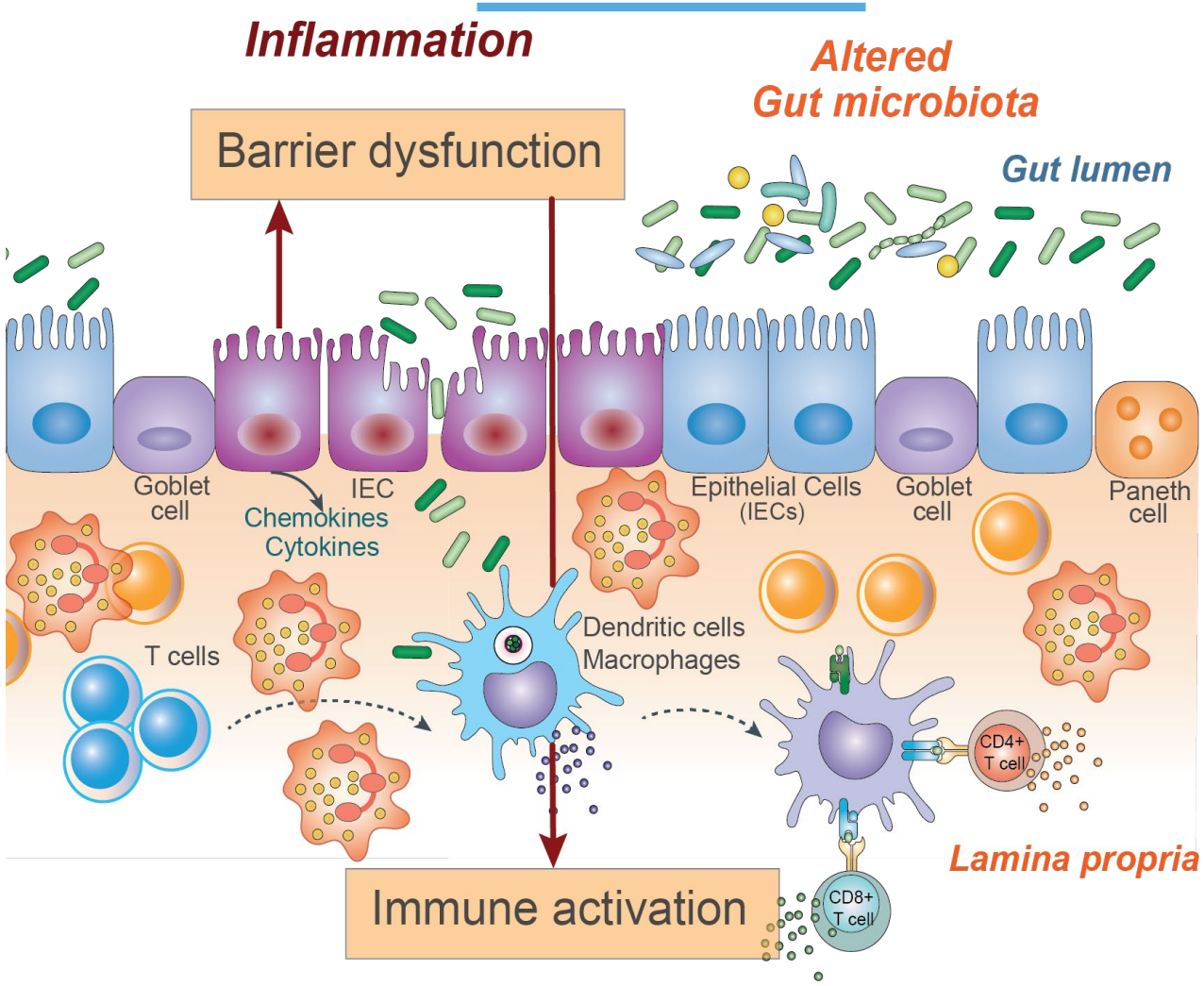
Disclosures

All authors were Synlogic employees and shareholders at the time the work was performed.

Intestinal Homeostasis is Disrupted in IBD

Disease pathophysiology in IBD linked to compromised barrier function and increased inflammation



Mucosal healing is the next therapeutic goal to achieve stable remission in IBD patients

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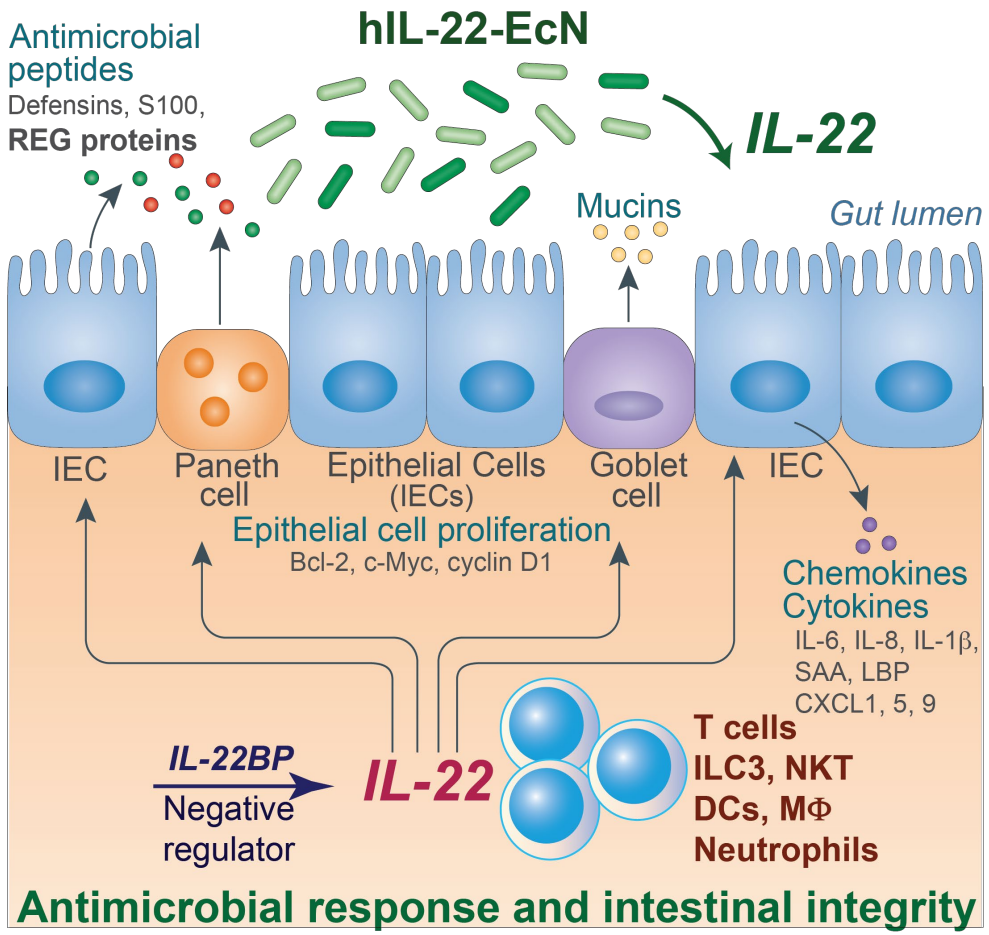
Zhang 2017, Neurath 2014, Bourma and Strober 2003

IL-22 as a Therapeutic Effector

Promotes barrier function and mucosal healing



Adapted from Keir et al., 2020

- IL-22 promotes epithelial barrier functions and mucosal healing.
- Extensive pre-clinical evidence supports a critical role for IL-22 in IBD.
- Many IL-22 associated molecules are encoded by IBD susceptibility genes and patients with ulcerative colitis have evidence of IL-22 dysfunction.
- Systemically administered hIL-22-Fc results in pharmacodynamic responses but is associated with dose-dependent skin adverse effects.

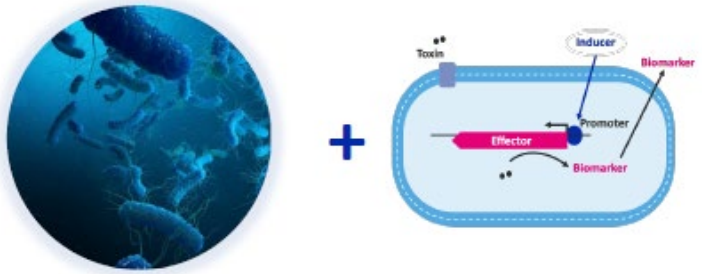
Can local delivery of IL-22 in the gut promote epithelial barrier healing in IBD patients without systemic toxicity?

Rutz 2014, Chi 2014, Wang 2014 , Stefanich 2018, Sugimoto 2008, Rothenberg 2018

Synthetic Biotics: A Novel Approach to Immune Diseases

Exploiting the Interaction Between Bacteria and the Immune System

Synthetic Biotic platform



Non-pathogenic bacterial chassis

\+

Programable, engineering

Targeted & controllable, **patient friendly** treatment

Bacteria and Immune System are Intimately Linked

- Immune system has evolved to recognize bacteria
- Bacteria have evolved mechanisms to control the immune response

Synthetic Biotics Enable Unique Therapeutic Opportunities

- Bacteria has evolved to survive the gastrointestinal tract
- Local delivery to the site of disease

Synthetic Biotics Enable Multiple Therapeutic Modalities

- Ability to deploy multiple pathways
- Broad expression of bacterial and mammalian effectors

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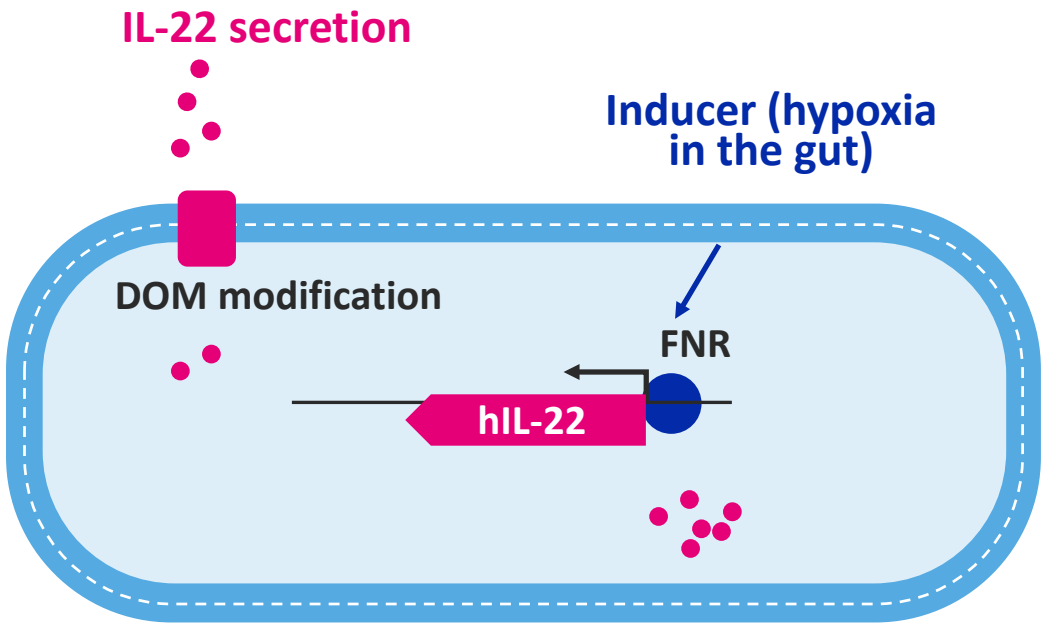
Engineering *E. coli* Nissle to Secrete hIL-22

Component	Benefit
e. coli Nissle	Probiotic: Decades of human use & safety data
hIL-22	Improvement of epithelial barrier health
FNR promoter	Induced by lack of oxygen in the gut
Secretion system	Diffusible outer membrane (DOM) to enable protein secretion



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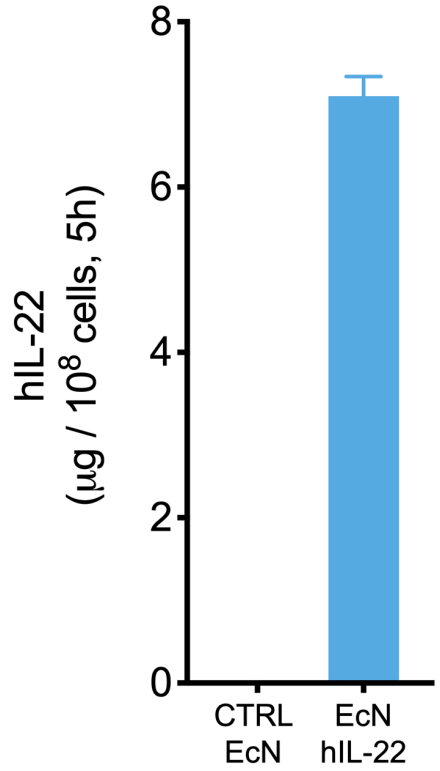
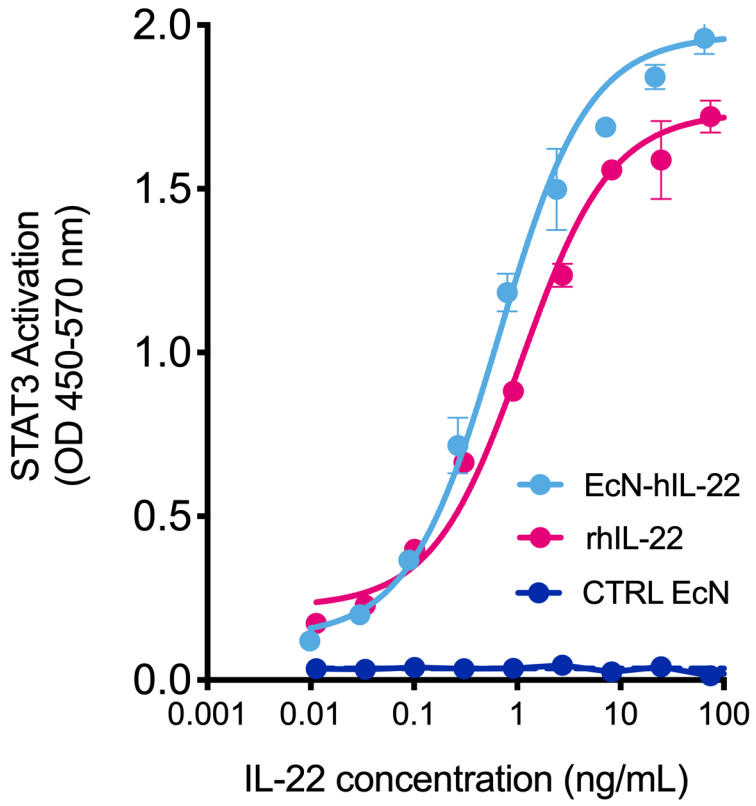
Engineered EcN Produces IL-22 with Comparable Bioactivity to rhIL-22

In vitro Characterization of EcN-hIL-22

hIL-22 Production



hIL-22 Bioactivity



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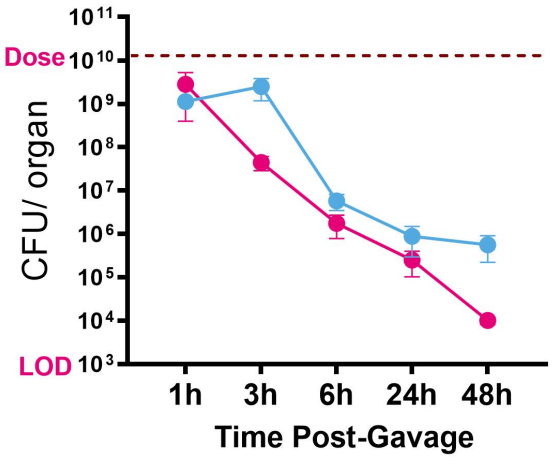
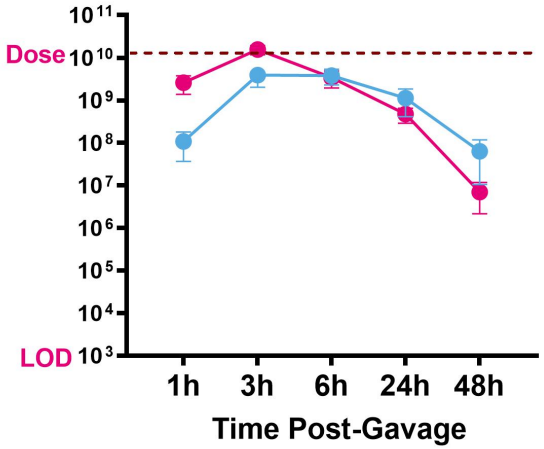
EcN-hIL-22 is Viable in the Gut of DSS-treated mice

In vivo kinetics of a single dose, 1e10 CFUs/ mouse

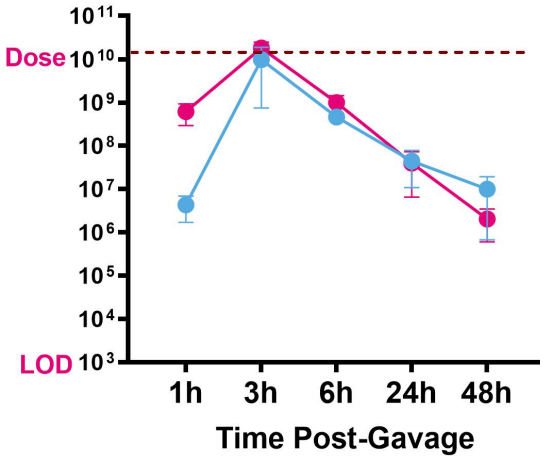
Small intestine



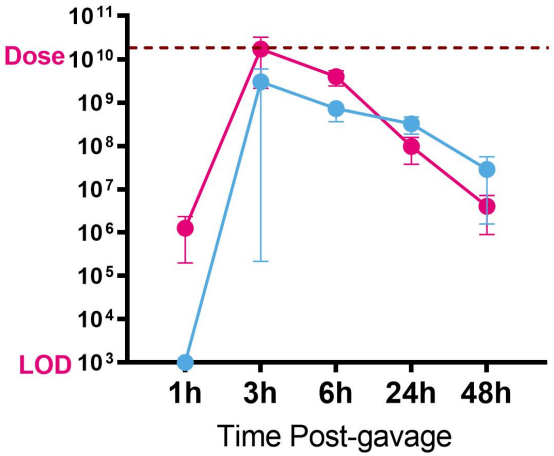
Cecum



Colon



Feces



cN-hIL-22

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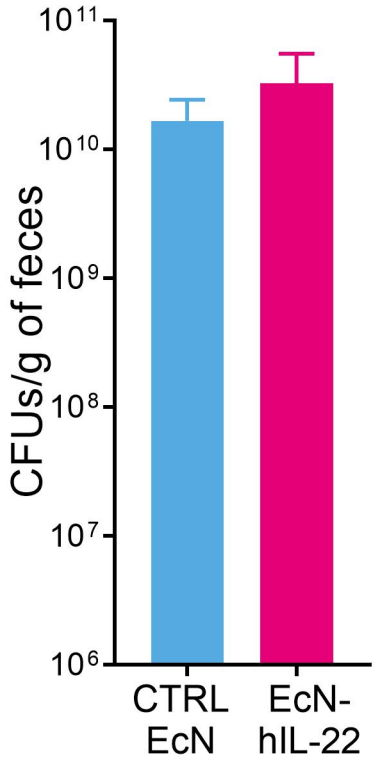
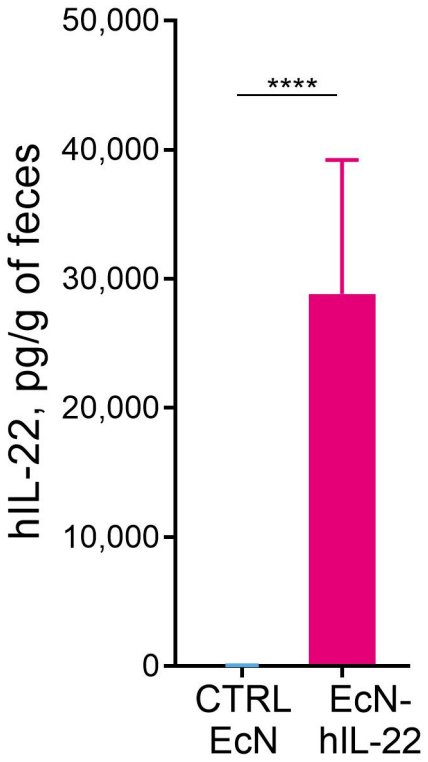
EcN-hIL-22 is Active in the Colon of DSS-treated Mice

In vivo cytokine production 6 hours after a single dose, 1e10 CFUs/ mouse

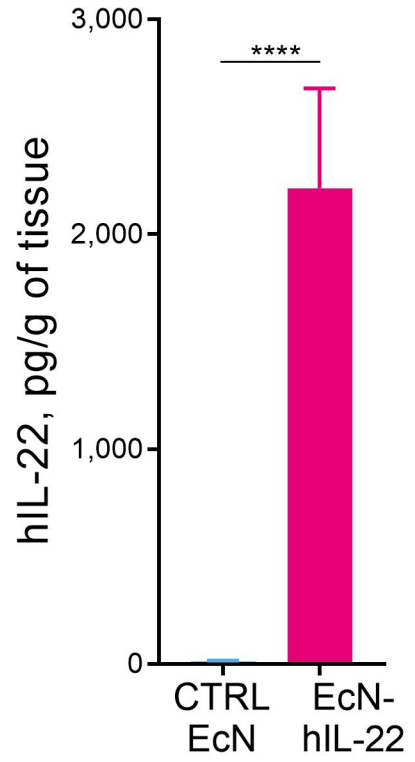
Fecal CFU



Fecal hIL-22



Colon hIL-22



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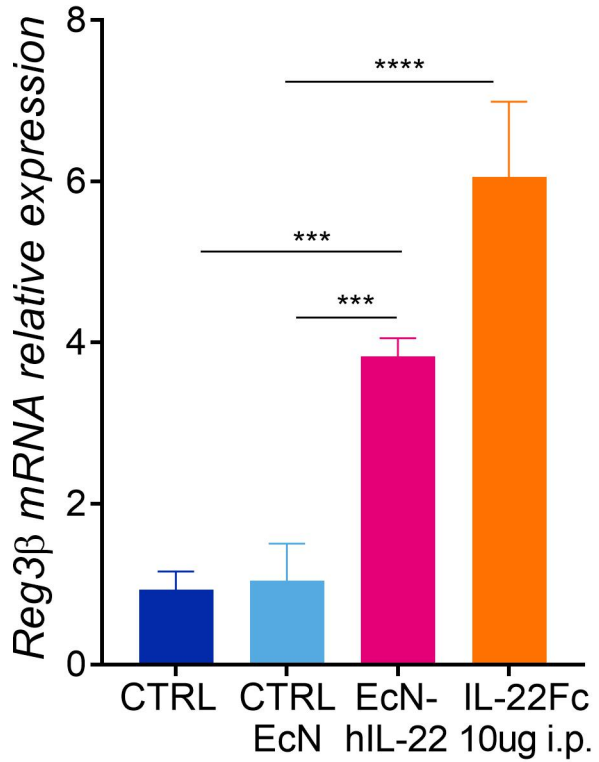
Strain Delivers Biologically Active hIL-22 to the Inflamed Gut

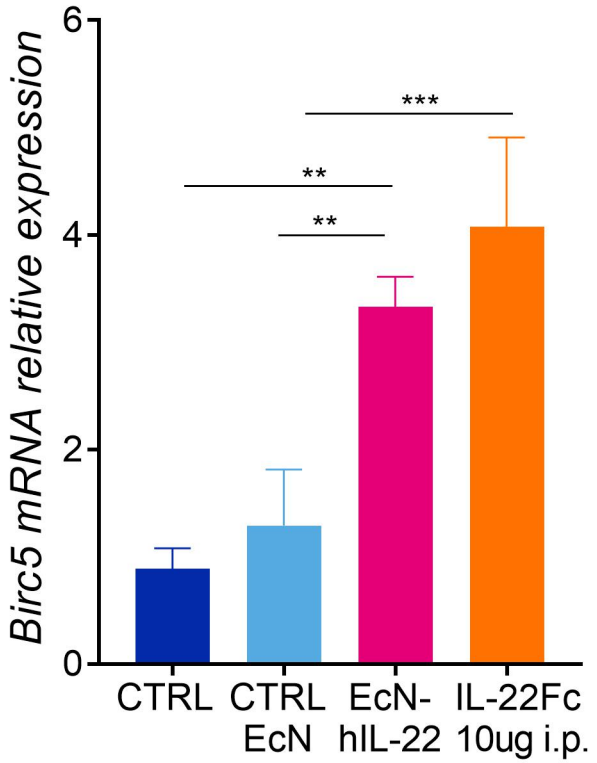
In vivo target engagement after prolonged bacterial exposure (up to 24h)

Colon Reg3β mRNA



Antimicrobial

Colon Birc5 mRNA



Anti-apoptotic

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Summary and Conclusions

Engineered probiotic *E.coli* Nissle strain produces bioactive human IL-22

Summary

- Engineered EcN secretes high levels of bioactive hIL-22 *in vitro*.
- EcN-hIL-22 is viable in different compartments of the mouse inflamed gut.
- EcN-hIL-22 secretes high levels of hIL-22 in inflamed colon:
  - hIL-22 detected in feces and colon.
- Bacterially produced hIL-22 is bioactive in the gut:
  - Target engagement in inflamed colonic tissue.

Conclusions

- Engineered EcN has the potential to deliver hIL-22 locally in the gut to improve mucosal healing and achieve remission in IBD patients while preventing the adverse effects associated with systemic delivery of the protein.
- These data support the development of Synthetic Biotic medicines as a novel approach to treat intestinal immune-mediated diseases.