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Debugging Crohn's disease

By Benjamin Boettner, Assistant Editor

The intestinal flora of patients with Crohn's disease is frequently populated by adherent-invasive *Escherichia coli*, which cause intestinal inflammation. Although this inflammatory response is typically treated with tumor necrosis factor–lowering therapies, **University of Nantes Angers Le Mans** researchers have gone right to the source and targeted the bacteria directly with modified mannosides.[1] The researchers are planning to assess the compounds in a chronic mouse model for the disease.

CD is caused by a group of infectious bacterial strains that trigger a tumor necrosis factor (TNF)-induced inflammatory response. Patients experience a shift in the composition of their enteric microbiota, called dysbiosis,[2,3] that is associated with overexpression of *carcinoembryonic antigen–related cell adhesion molecule 6* (*CEACAM6*; *NCA*; *CD66c*).[4]

CEACAM6 presents oligomannosides on the surface of intestinal epithelial cells. These oligomannosides allow adherent-invasive *E. coli* (AIEC), which are part of the intestinal microbiome in about 33% of patients with CD, to bind to the cells via a surface adhesion protein called fimbrial adhesin (fimH).

Marketed CD drugs suppress the inflammatory response by lowering TNF levels. The three anti-TNF antibodies on the market for CD are Humira adalimumab from **AbbVie Inc.**, Remicade infliximab from **Johnson & Johnson** and Cimzia certolizumab pegol from **UCB Group**.

Recent data have shown that about 60% of patients responded to Humira, and of those, only 25% remained in remission after 1 year.[5]

A team led by Sébastien Gouin, research investigator at the **Centre National de la Recherche Scientifique** (CNRS) at the University of Nantes Angers Le Mans (L'UNAM), hypothesized that targeting the CD-causing bacteria rather than the secondary inflammatory response could provide an alternative therapy.

Gouin's group is no stranger to AIECs. His team and others have used synthetic, mannoside-based antagonists to target fimH in a different condition caused by AIECs—urinary tract infection (UTI).[6,7]

The L'UNAM team developed a new class of *N*-linked thiazolylamino-mannosides that antagonized fimH *in vitro* and inhibited AIEC attachment in an *ex vivo* model of CD. The new mannosides inhibited attachment of AIECs to colonic explants obtained from a mouse model for CD in which *Ceacam6* is overexpressed in the ileum.[8]

Data were published in the *Journal of Medicinal Chemistry*.

"As far as I know, our results suggest for the first time the possibility to use synthetic mannosides to treat CD," said Gouin.

"This work approaches CD treatment from a microbiological lens—focusing on a pathogen potentially linked to the pathophysiology of the diseases instead of the current paradigm in the field of focusing primarily on blocking proinflammatory mediators," said Bernat Olle, COO of **Vedanta Biosciences Inc.** and a principal at **PureTech Ventures**. "In this sense, the approach is differentiated from and could be complementary to current drugs."

Vedanta is developing an oral formulation of enteric bacteria to reduce the proportion of inflammation-inducing agents that occur in inflammatory bowel disease (IBD).

"Mannosides, provided side effects are minimal or tolerable, could prove a major advance over current immune modulatory treatment strategies for CD, which can have long-term side effects," said Renate Kain, a professor at the **Medical University of Vienna** who has studied fimH-expressing AIECs in necrotizing glomerulonephritis.[9]

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>
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Anti-TNF treatments can increase the risk of both infection and certain cancers such as melanomas and non-Hodgkin's lymphoma.

Taking (manno)sides

Gouin's team plans to enhance the potency of the mannosides by generating multivalent scaffolds that combine several individual mannosides in one molecule. The team has previously developed multivalent mannosides to target uropathic *E. coli*.[10]

Although the mannosides described in the paper have shown strong effects in *in vitro* and *ex vivo* experiments, an unanswered question is whether resistance will develop.

Gouin's team plans to test the effects of the mannosides on chronic AIEC infection and other CD features in the *Ceacam6* mouse model for CD.

Alain Vicari and Yolande Chvatchko told *SciBX* that chronic AIEC infection in streptomycin-treated conventional mice, an alternative model for CD,[11] could complement the *Ceacam6* model in gauging the *in vivo* effects of the compounds independently of *Ceacam6* overexpression. Vicari and Chvatchko are founders of **Calypso Biotech S.A.** and share the title of VP of R&D.

Vicari wanted to see how the effects of the compounds translate from *in vitro* systems to *in vivo* animal models to humans, especially considering the differences in intestinal physiology and the complexity of the gut microbiome.

Calypso, a spinoff of **Merck KGaA**'s **Merck Serono S.A.** unit, is developing an antibody-based therapy against an undisclosed target for a fistulizing form of CD.

Olle said any *in vivo* studies should keep track of the effects of the mannosides on beneficial commensal bacteria.

Another potential complication is that variants of fimH that differ by specific point mutations could be differentially sensitive or even resistant to specific mannoside compounds. Mutations in fimH result in structural differences that affect colonization and thus the inflammation-inducing potential of AIECs.[12]

Gouin told *SciBX* that he plans to analyze the specificity of the published mannoside collection for different fimH variants and determine which mutants might be most sensitive to specific mannoside compounds.

"By analyzing genetic variants in the AIEC *fimH* from patients, in the future it could become possible to design tailored treatments for particular subsets of patients," said Chvatchko.

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Olle added that future clinical trials and more personalized treatment options would also benefit from the discovery of intestinal biomarkers that indicate the presence of AIECs in patient samples. Prescreening for such biomarkers would help identify which patients could benefit from mannoside treatments.

Jim Janetka, professor at the **Washington University in St. Louis School of Medicine** and cofounder and scientific advisor of **Fimbrion Therapeutics Inc.**, told *SciBX* that achieving clinically useful bioavailabily with compound sugars such as modified mannosides can be a considerable challenge because of their often insoluble nature.

Gouin confirmed to *SciBX* that the most promising compounds will be subject to complete cytotoxic and pharmacokinetic evaluation. He said that the most promising compound of the collection is water soluble. He added that less water-soluble compounds can be modified by the addition of hydrophilic groups.

Fimbrion is developing fimH-targeting therapies for UTI.

Gouin said CNRS has filed for a patent covering the findings and the IP is available for licensing.

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REFERENCES

1. Brument, S. *et al. J. Med. Chem.*; published online June 12, 2013; doi:10.1021/jm400723n
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2. Scanlan, P.D. *et al. J. Clin. Microbiol.* **44**, 3980–3988 (2006)
3. Manichanh, C. *et al. Gut* **55**, 205–211 (2006)
4. Barnich, N. *et al. J. Clin. Invest.* **117**, 1566–1574 (2007)
5. Allen, P.B. & Peyrin-Biroulet, L. *Curr. Opin. Gastroenterol.* **29**, 397–404 (2013)
6. Cusumano, C.K. *et al. Sci. Transl. Med.* **3**, 109ra115 (2011)
7. Klein, T. *et al. J. Med. Chem.* **53**, 8627–8641 (2010)
8. Chan, C.H.F. & Stanners, C.P. *Mol. Ther.* **9**, 775–785 (2004)
9. Kain, R. *et al. Nat. Med.* **14**, 1088–1096 (2008)
10. Gouin, S.G. *et al. ChemMedChem* **4**, 749–755 (2009)
11. Small, C.-L.N. *et al. Nat. Commun.* **4**, 1957 (2013)
12. Dreux, N. *et al. PLoS Pathog.* **9**, e1003141; published online Jan. 24, 2013; doi:10.1371/journal.ppat.1003141

COMPANIES AND INSTITUTIONS MENTIONED

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