Received: 19 May 2021 | Revised: 27 August 2021 | Accepted: 26 September 2021

DOI: 10.1111/cts.13179

LETTER TO THE EDITOR

Predictive approaches in inflammatory bowel disease

Dear Editors,

The authors report the successful development of a mathematical model of inflammatory bowel disease (IBD) structured in two compartments and combining ulcerative colitis (UC) and Crohn's disease (CD).[1]

IBDs are multifacets and multi-omics diseases.[2]

Different features contribute to responsiveness to treatments and would need to be carefully considered in parametric predictive models. The immune system presents some plasticity, and one clinical phenotype can activate different inflammatory pathways and respond differently to therapies.

As introduced by the authors, UC and CD are two heterogeneous and different diseases, for which immunology is a backbone but not identical.[1,3] Their biology is different and leads to different diagnosis, treatment, and monitoring approaches.[4] The application of the model to CD therapies is provided.[5]

Current data suggest that CD is a multiple entity—inflammation is not homogeneous along the colon—and that interleukins pathways and mechanisms of action of potential treatments implicate several tissue layers.[1–3]

An alternative to the proposed model would be then five gut compartments: ileum, ascending, transverse, descending colon, and sigmoid colon–rectum, each divided into subepithelial tissues, lymph nodes, and epithelium. It would allow tissue level spatial considerations for inflammation. Gut compartments would be connected through the blood compartment, and each would have associated epithelial and mucosal layers. The epithelial layer would be healthy, active, damaged, or remodeled. Active and damaged layers would possibly revert but remodeled would be irreversible. Active, damaged, and remodeled tissue fractions would generate SES-CD subscores. Inflammation would be estimated by serum C-reactive-protein and fecal calprotectin. Detailing the intestinal epithelial barrier (IEB) would increase the model prediction accuracy: IEB healing impacts the inflammation level.[1]

The mechanistic component is key in modeling. It brings (a) ability to generalize the learning from a patient's response to one treatment and to extrapolate likely responsiveness to different regimens or drugs, (b) flexibility to challenge multiple short-term and long-term treatment options, and (c) transparency compared to the black-box type machine learning approach.

As stated by the authors, the model reasonably replicates cytokines, cells, and biomarkers steady-state values in IBD. Its simplified approach helps mapping the diseases but with some limitation in treatment strategies evaluation.[5] The use of artificial intelligence has recently grown in IBD.[6] Alternative models will soon emerge.

Understanding how individual patients respond (outcomes and related paths) to treatments is critical to improve IBD management. Available treatments, including biologics, do not break a 40%-to-60% efficacy ceiling.[7] Hopefully models will help.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST

P.P. is an employee of Ferring Pharmaceuticals and owns stocks of Takeda Pharmaceutical Company Limited.

Philippe Pinton

Translational Medicine and Clinical Pharmacology, Ferring Pharmaceuticals A/S, International PharmaScience Center, Copenhagen S, Denmark

Correspondence

Philippe Pinton, Ferring Pharmaceuticals A/S, International PharmaScience Center, Kay Fiskers Plads, 111200 Copenhagen S, Denmark.
Email: philippe.pinton@ferring.com

ORCID

Philippe Pinton https://orcid.org/0000-0002-4227-7687

Reference to the manuscript published in the January 2021 issue: Katharine V. Rogers, Steven W. Martin, Indranil Bhattacharya, Ravi Shankar Prasad Singh, and Satyaprakash Nayak. A dynamic quantitative Systems pharmacology model of inflammatory bowel disease: part 1 – model framework. *Clin Transl Sci.* 14: 239–248 (2021).

REFERENCES

1. Rogers KV, Martin SW, Bhattacharya I, Singh RSP, Nayak S. A dynamic quantitative Systems pharmacology model of inflammatory bowel disease: part 1 – model framework. *Clin Transl Sci*. 2021;14:239-248.
2. Privitera G, Pugliese D, Rapaccini GL, Gasbarrini A, Armuzzi A, Guidi L. Predictors and early markers of response to biological therapies in inflammatory bowel diseases. *J Clin Med*. 2021;10:853-873.
3. Atreya R, Siegmund B. Location is important: differentiation between ileal and colonic Crohn's disease. *Nat Rev Gastroenterol Hepatol*. 2021;18:544-558.
4. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology*. 2021;160(5):1570-1583.
5. Rogers KV, Martin SW, Bhattacharya I, Singh RSP, Nayak S. A dynamic quantitative Systems pharmacology model of inflammatory bowel disease: part 2 – Application to Current Therapies in Crohn's Disease. *Clin Transl Sci*. 2021;14:249-259.
6. Gubatan J, Levitte S, Patel A, Balabanis T, Wei MT, Sinha SR. Artificial intelligence applications in inflammatory bowel disease: emerging technologies and future directions. *World J Gastroenterol*. 2020;17:1920-1935.
7. Seyed Tabib NS, Madgwick M, Sudhakar P, Verstockt B, Korcsmaros T, Vermeire S. Big data in IBD: big progress for clinical practice. *Gut*. 2020;8:1520-1532.