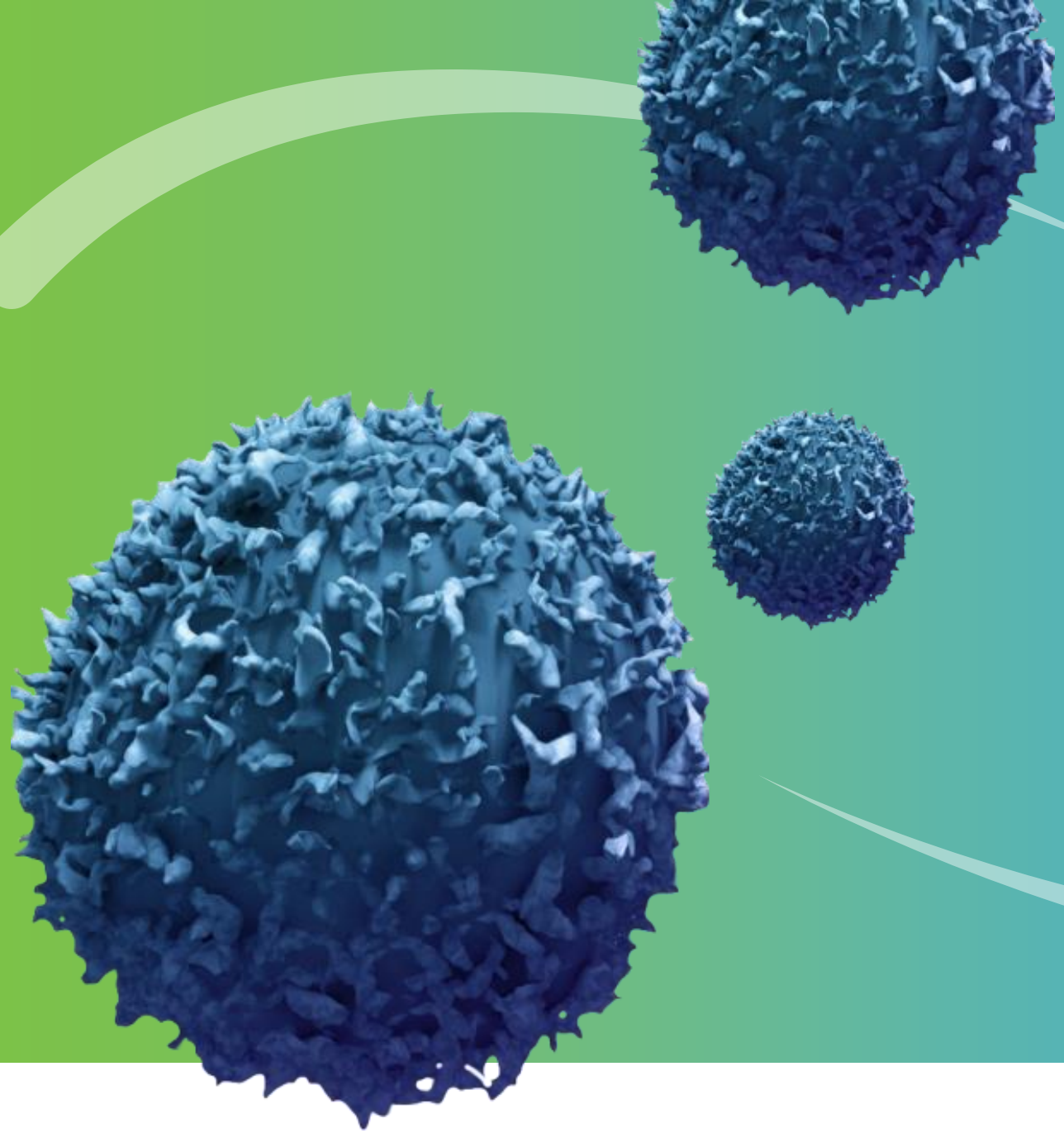


Virtual KOL Event to Discuss EQ504: A Novel Aryl Hydrocarbon Receptor (AhR) Modulator for Ulcerative Colitis

November 5, 2025

Forward-Looking Statements and Other Disclaimers

This presentation contains forward-looking statements about Equillium, Inc. (the "Company"). In some cases, you can identify forward-looking statements by the words "will," "expect," "intend," "plan," "objective," "believe," "estimate," "potential," "continue" and "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements are based on Company management's current beliefs and expectations. These statements include but are not limited to statements regarding the Company's business strategy, the Company's plans to develop and commercialize its product candidates, the safety and efficacy of the Company's product candidates, the Company's plans and expected timing with respect to regulatory filings and approvals, size and growth potential of the markets for the Company's product candidates and cash runway. These statements involve known and unknown risks, uncertainties and other factors that may cause the Company's actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. The Company may not actually achieve the plans, intentions or expectations disclosed in its forward-looking statements, and you should not place undue reliance on the Company's forward-looking statements.

Actual results or events could differ materially from the plans, intentions and expectations disclosed or implied in the forward-looking statements the Company makes due to the risks and uncertainties inherent in the Company's business, including without limitation, the risks described in the Company's filings with the Securities and Exchange Commission ("SEC"). You are cautioned not to place undue reliance on these forward-looking statements, which represent the Company's views as of the date of this presentation. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company has no current intention of doing so except to the extent required by applicable law. These and other risks and uncertainties are described more fully under the caption "Risk Factors" and elsewhere in the Company's filings and reports, which may be accessed for free by visiting EDGAR on the SEC web site at http://www.sec.gov and on the Company's website under the heading "Investors." All forward-looking statements are qualified in their entirety by this cautionary statement. This caution is made under the "safe harbor" provisions of Section 21E of the Securities Exchange Act of 1934, as amended.

This presentation may contain trademarks, service marks, trade names and copyrights of other companies, which are the property of their respective owners. Solely for convenience, some of the trademarks, service marks, trade names and copyrights referred to in this presentation may be listed without the TM, SM © or ® symbols, but Equillium will assert, to the fullest extent under applicable law, the rights of the applicable owners, if any, to these trademarks, service marks, trade names and copyrights.

This presentation discusses product candidates that are under clinical study, and which have not yet been approved for marketing by the US Food and Drug Administration. No representation is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied. Caution should be exercised when comparing data across trials of different products and product candidates, as significant differences may exist between trial designs, patient populations and other study characteristics. Furthermore, the results across such trials may not have interpretative value on our existing or future results.

Today's Agenda

Introduction	**Bruce Steel, CFA**
The aryl hydrocarbon receptor: A target for immune modulation	**Francisco J. Quintana, PhD**
Emerging Therapies 2025	**Brian Feagan, MD, FRCPC**
EQ504: Targeting AhR to Promote Mucosal Healing In Ulcerative Colitis	**Stephen Connelly, PhD**
Q&A Session	**Management & KOLs**

Introduction: Francisco J. Quintana, PhD

Francisco J. Quintana, PhD holds the Kuchroo Weiner Distinguished Chair in NeuroImmunology at Harvard Medical School and an Associate Member at the Broad Institute of Harvard and MIT. Dr. Quintana's research investigates signaling pathways that control the immune response with the ultimate goal of identifying novel therapeutic targets and biomarkers for immune-mediated disorders. He is well known for his research on the role of the Aryl Hydrocarbon Receptor (AhR) identifying important roles for the transcription factor in the control of inflammation driven. Key contributions include studies on the role of AhR in modulating effector and regulatory T cell functions through IL-10 and IL-22, both play an important role in mucosal immunology. Working with Dermavant, Dr. Quintana was involved in the development of Tapinarof (VTAMA®), the first FDA-approved AhR modulator for the treatment of both psoriasis and atopic dermatitis. Overall, Dr. Quintana's research has on AhR has implications in our understanding of the pathology and treatment of multiple autoimmune and inflammatory disorders. Dr. Quintana has published over 230 peer reviewed articles and book chapters. In addition, Dr. Quintana's research has resulted in multiple patents which have been the foundation of four companies: ImmunArray Ltd, Alma Bio Therapeutics, AnTolRx Inc, and Violet Therapeutics. Dr. Quintana is the Director of the course Autoimmunity at Harvard Medical School. Dr. Quintana has been the recipient of the Lady Anne Chain Prize for Academic Excellence and Scientific Achievements, the Junior Investigator Award from the National Multiple Sclerosis Society, the Pathway to Independence Award of the National Institute of Allergy and Infectious Diseases, the Award for Outstanding Research Achievements form Nature Biotechnology and the Tecan Award for Innovation, the Harry Weaver Award from the National Multiple Sclerosis Society, the Young Mentor Award from Harvard Medical School, the Milestones in MS research from the National MS Society, the AAI-BD Bioscience Investigator Award, the Barancik Prize for Innovation in MS Research from the National Multiple Sclerosis Society, and the Raices Award from the Republic of Argentina. He has been listed as one the Most Highly Cited researchers by the Institute for Scientific Information (ISI) every year since 2019, and has been the Indirawati Kuchroo and Charlotte Weiner Distinguished Professor of Neuroimmunology at Brigham and Women's Hospital and Harvard Medical School since 2021.

The aryl hydrocarbon receptor: A target for immune modulation

Francisco J. Quintana

Harvard Medical School

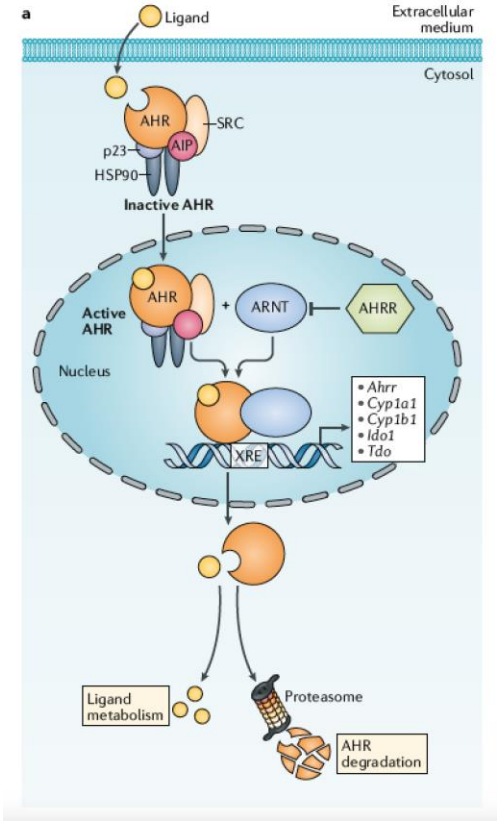
Broad Institute of MIT and Harvard

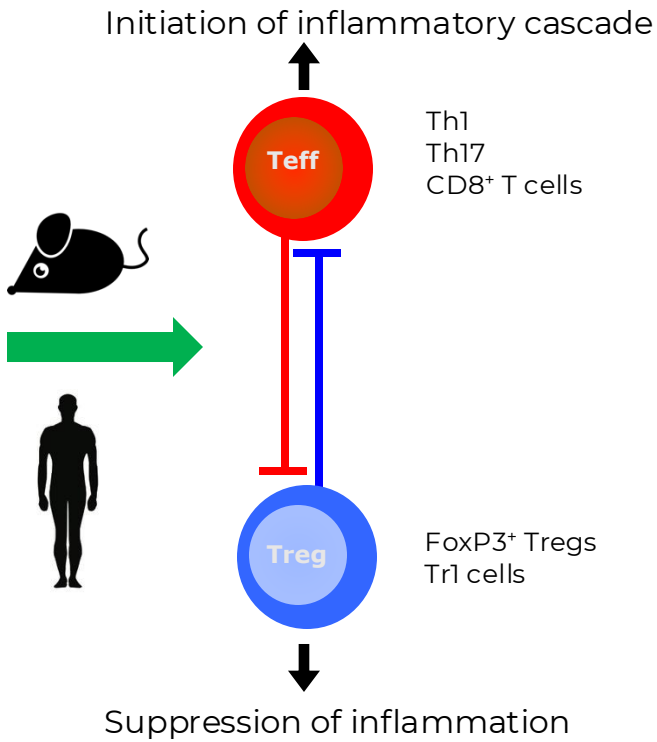
Fishing for Novel Regulators of the Immune Response

Circa 2005

The Aryl Hydrocarbon Receptor (AHR)

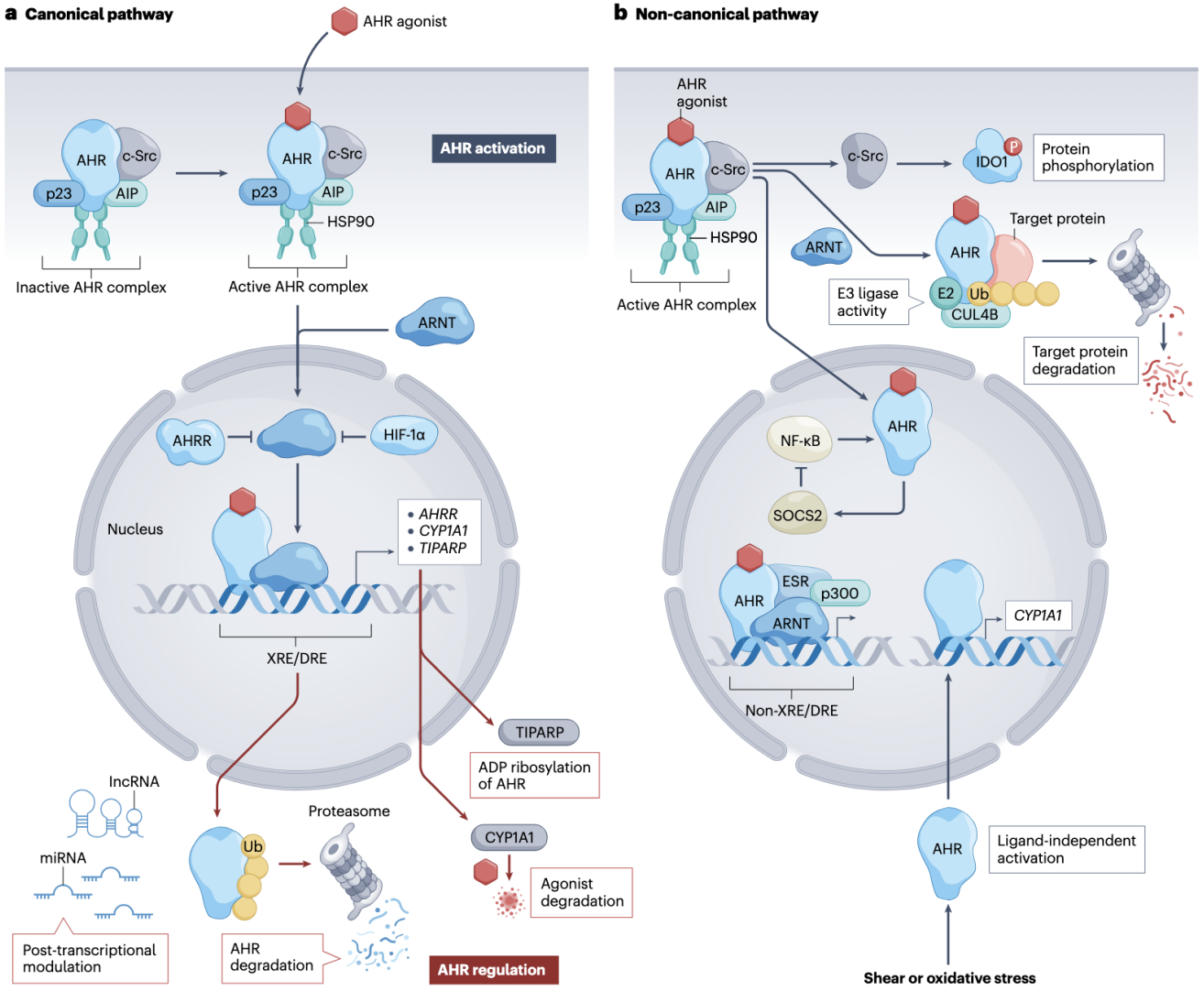
Quintana et al, Nature 2008





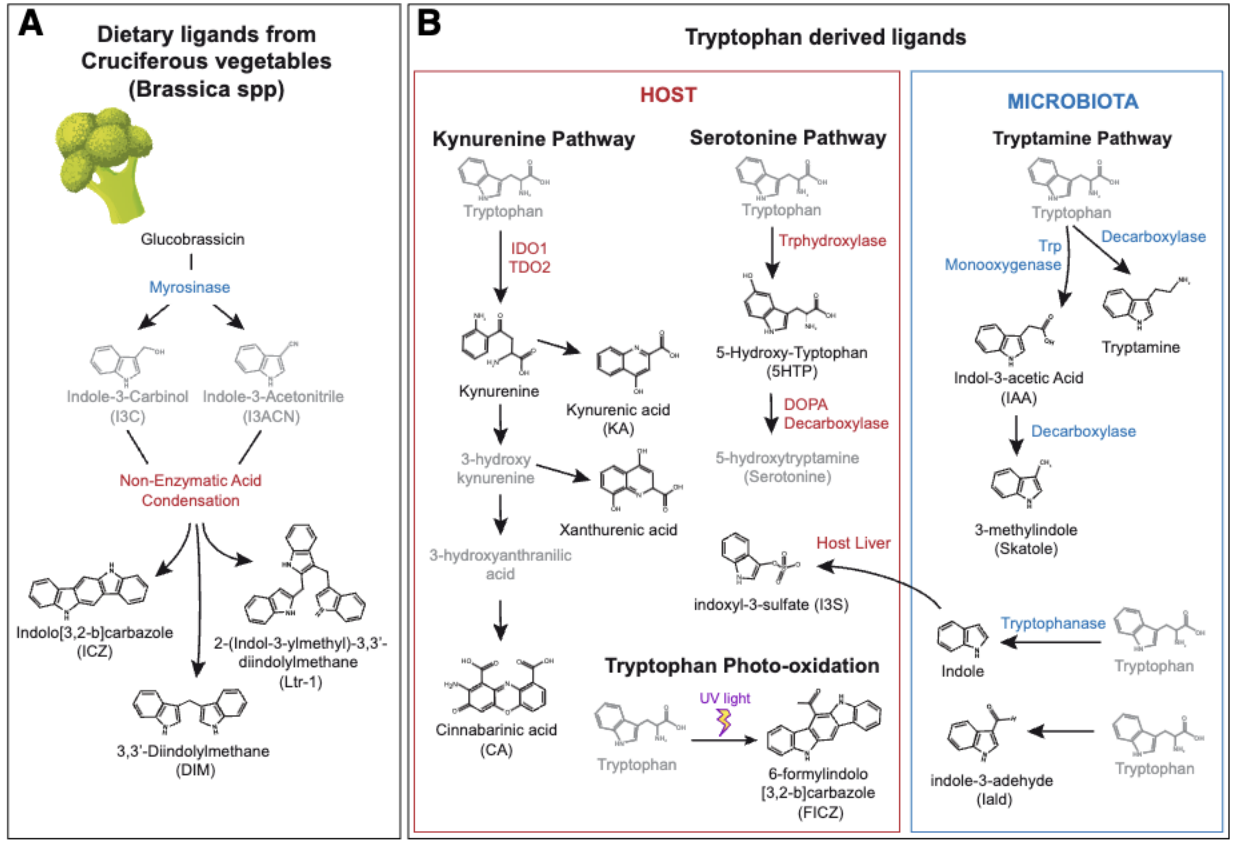
Nature (2008); Nat. Immunology (2010); Nat. Immunology (2010); PNAS (2010); PLoS One (2010); PNAS (2012); Nat. Immunology (2012); Nat. Immunology (2012); Nat. Immunology (2013); Nat. Communications (2014); Cell (2015);Nat. Medicine (2015); Cell reports (2016a); Cell reports (2016b); Science Signaling (2016); Nat. Neuroscience (2019); PNAS (2020); Nature Neuroscience (2020); Nature) Communications (2021); PNAS (2021); Nature (2022); Nature Cancer (2023); Nature (2025a); Nature (2025b)

AHR Signaling



Polonio and Quintana, Nature Reviews in Drug Discovery 2025

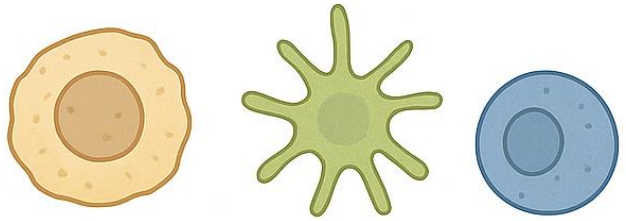
AHR Physiologic Agonists



Gutierrez-Vazquez and Quintana, Immunity 2018

AHR Responsive Cells in the Gut

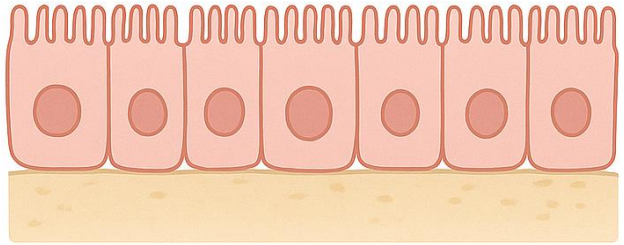
Immune Cells



<u>Immune homeostasis & tolerance</u>

- Innate Lymphoid Cells
- Dendritic Cells & Macrophages
- Effector T Cells
- Regulatory T Cells

Non-immune Cells



<u>Maintain Barrier Function</u>

- Intestinal Epithelial Cells
- Goblet Cells
- Paneth Cells

IL-10 and IL-22 in Mucosal Biology

IL-10

Immuno-modulatory peacekeeper

- Inhibits production of pro-inflammatory cytokines from macrophages & dendritic cells
- Enhances function of regulatory T cells and prevents uncontrolled activation of Th1/17 cells
- Prevents excessive inflammation and protects tissues from immune-mediated damage
- Essential for tolerance to commensal gut microbiota, maintaining intestinal homeostasis and preventing colitis

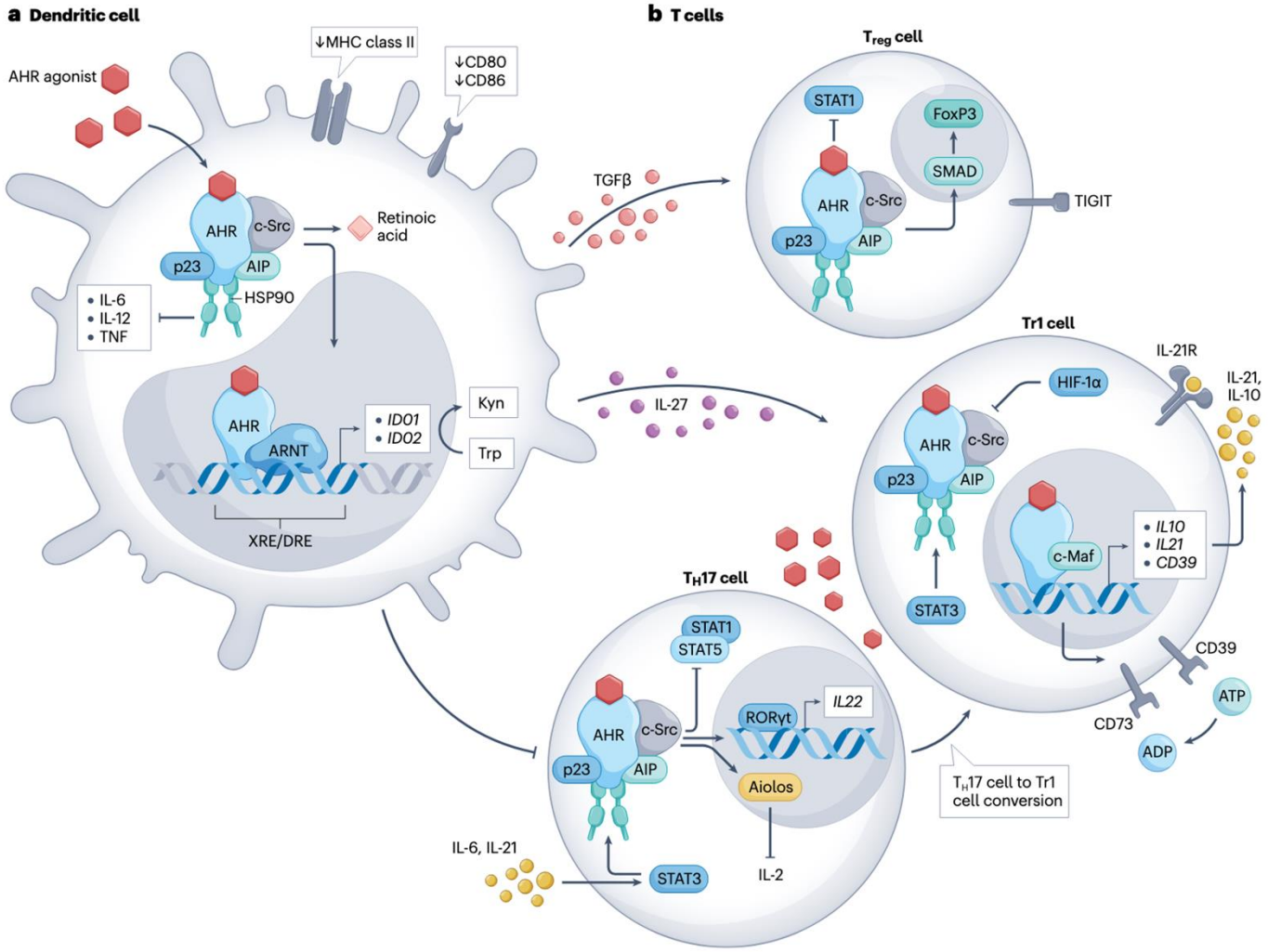
IL-22

Epithelial protector and healer

- Strengthens epithelial tight junctions to promote epithelial barrier integrity
- Stimulates proliferation, survival, and repair of intestinal epithelial cells
- Promotes wound healing and regeneration following injury or infection
- Induces antimicrobial peptides and strengthens host defense against pathogens at barrier sites

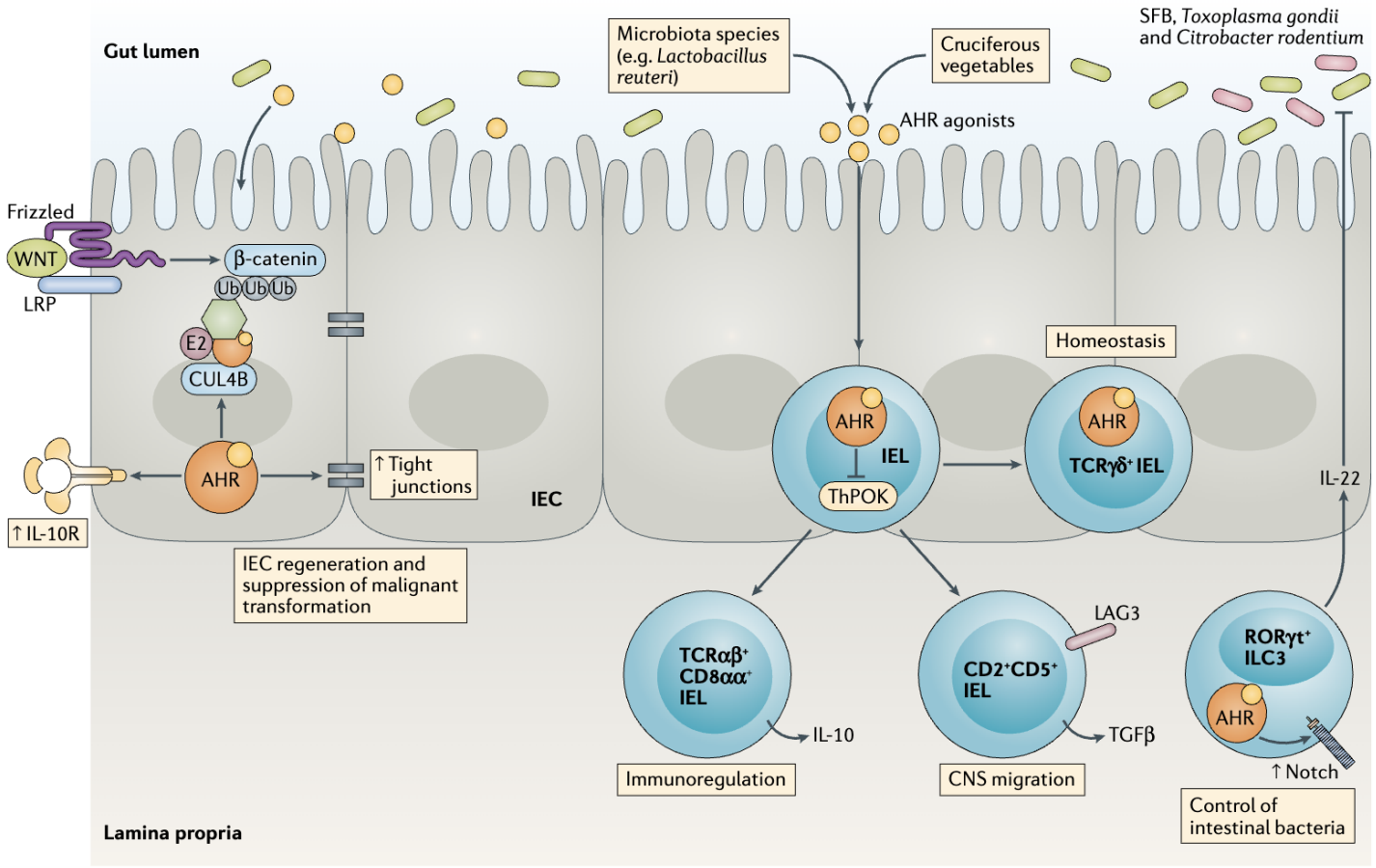
"IL-10 and IL-22 act together they maintain the immune-epithelial balance"

Regulation of Adaptive Immunity by AHR



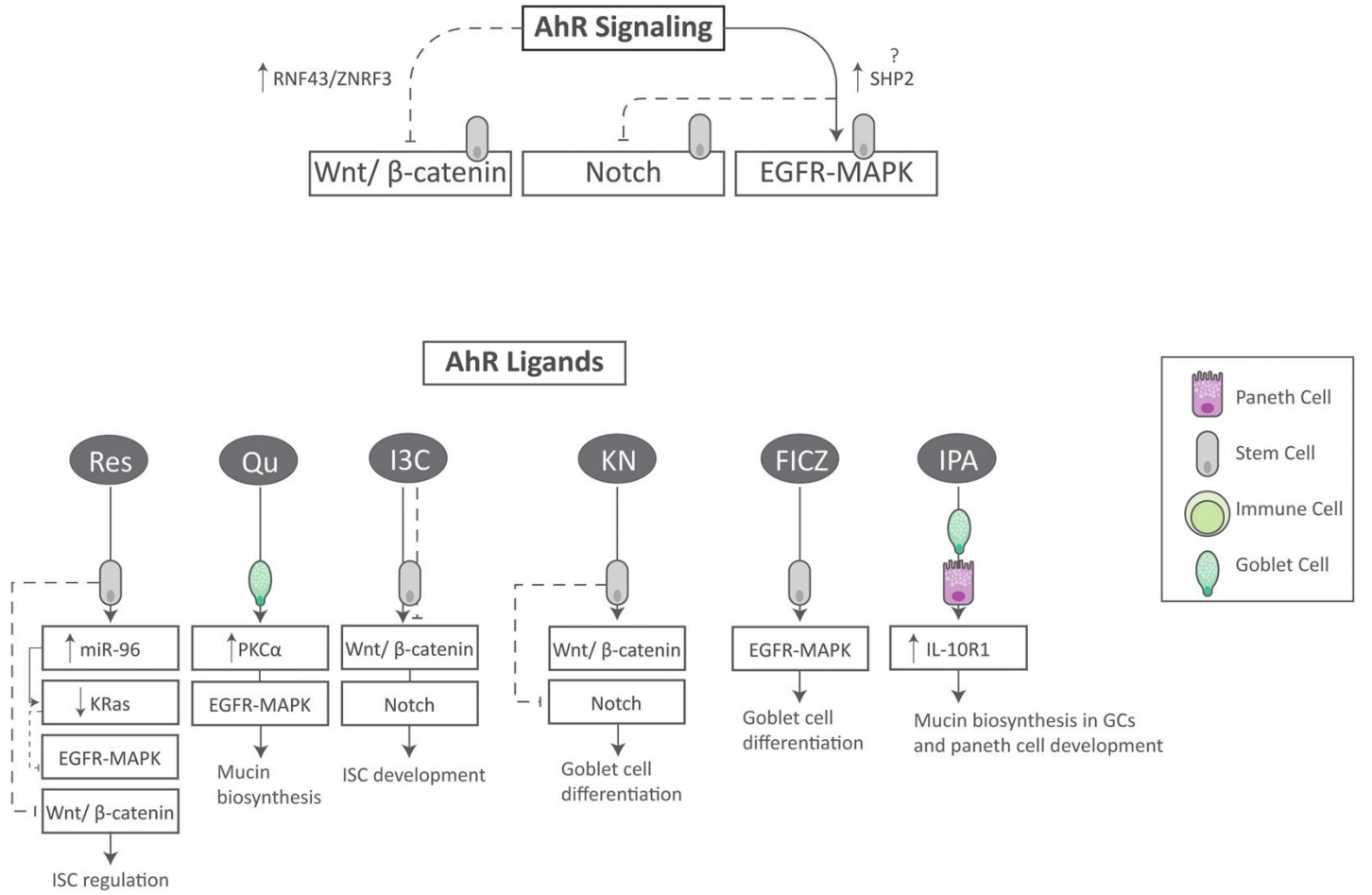
Polonio and Quintana, Nature Reviews in Drug Discovery 2025

Role of AHR in gut homeostasis



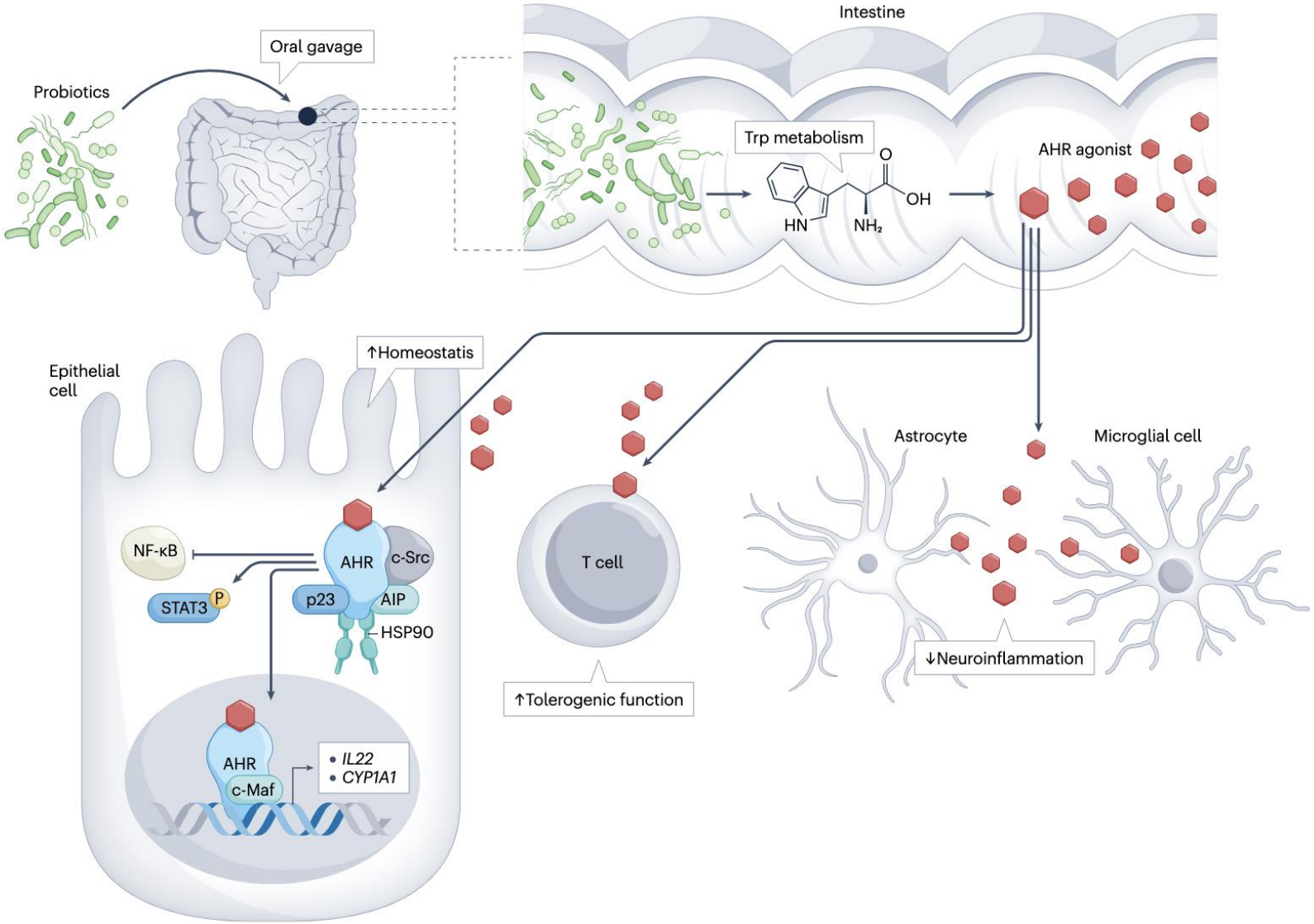
Rothhammer and Quintana, Nature Reviews in Immun. 19

Role of AHR in intestinal Stem Cells



Modified from Wisniweski et al, Frontiers in Immunology 2021

Therapeutic gut AHR activation



Polonio and Quintana, Nature Reviews in Drug Discovery 2025

Summary

- AHR regulates tissue inflammation and pathology through its effects on both immune and non-immune cells
- AHR limits pro-inflammatory responses
- AHR promotes the reestablishment of barrier integrity
- AHR regulates intestinal stem cell function
- AHR anti-inflammatory and tissue protective functions extend to other tissues beyond the gut.
- AHR an attractive therapeutic target with clinical validation

uintana Lab

fquintana@bwh.harvard.edu
Follow us in X: @QuintanalabHMS

Introduction: Brian G. Feagan, MD, FRCPC

Brian G. Feagan, MD, FRCPC is a gastroenterologist, with training in Clinical Epidemiology and Biostatistics. His research focus is the design, conduct and execution of large-scale randomized controlled trials (RCTs) in Crohn's disease (CD) and ulcerative colitis (UC), and over the past 30 years, has been Principal Investigator in over 140 multi-center RCTs. His research has been devoted to the development, validation and optimization of outcome measures to assess the efficacy of novel therapeutics in CD and UC. Dr. Feagan is Professor of Medicine at the Schulich School of Medicine & Dentistry, a gastroenterologist at London Health Sciences Centre and Senior Scientific Director of Alimentiv Inc (formerly Robarts Clinical Trials Inc). Dr. Feagan completed a medical degree at the University of Western Ontario (UWO) in London, Ontario, Canada. His postdoctoral training included a residency in Internal Medicine and a clinical fellowship in Gastroenterology in the Department of Medicine at UWO, and postgraduate training in the Department of Epidemiology and Biostatistics at McMaster University, Hamilton, Ontario. A Fellow of the Royal College of Physicians and Surgeons of Canada, Dr. Feagan holds membership in the Canadian and American Association of Gastroenterology, the American College of Gastroenterology, the College of Physicians and Surgeons of Ontario, Crohn's and Colitis Canada (CCC) and European Crohn's and Colitis Organization (ECCO). He has authored over 480 articles and book chapters and has given over 600 invited presentations at national and international scientific meetings. In 1997, Dr. Feagan became Director of Robarts Clinical Trials at the Robarts Research Institute, University of Western Ontario and in 2020, he became Senior Scientific Director of Alimentiv Inc.(formerly Robarts Clinical Trials) His research efforts focus on the design and implementation of randomized controlled trials of therapy for inflammatory bowel disease. He has been the principal investigator on numerous large-scale randomized clinical trials.

Emerging Therapies 2025:

Brian G. Feagan MD
Professor of Medicine, Epidemiology and Biostatistics
Western University
Senior Scientific Director, Alimentiv Inc.
London, Ontario, Canada

Disclosures

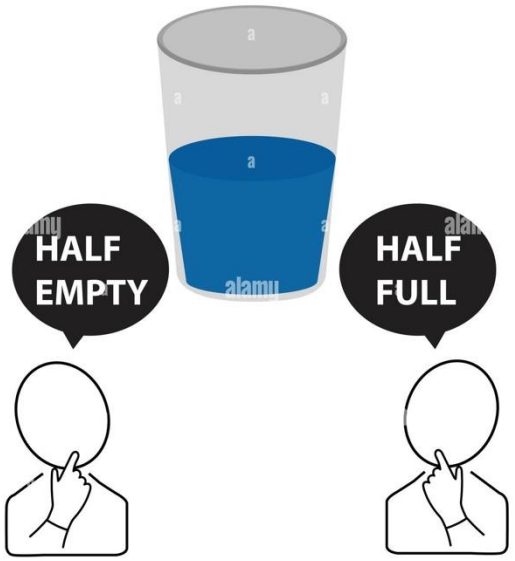
Grant/Research Support	
Consultant	AbbVie, Abivax, Adiso, AgomAB Therapeutics, Akros, Alira Health, Ally Bridge Group, AnaptysBio, Apini Therapeutics, Argenx, Avoro Capital Advisors, Belmore Law, BioFactura, BioJamp, Biora Therapeutics, Blackbird Laboratories, Boehringer-Ingelheim, Boxer Capital, Celsius Therapeutics, Celgene/BMS, Celltrion, Clarivate, Connect BioPharma, Disc Medicine, Duality, EcoR1, Eli Lilly, Ensho Therapeutics, Evida, Enveda, Faes Farma,First Wave, Forbion, Galapagos, Galen Atlantica, Genentech/Roche, General Atlantic, Genesis Therapeutics, Gilead, Gossamer Pharma, GSK, Imhotex, ImmiDomics, Immunic Therapeutics, Intercept, Janssen, Japan Tobacco Inc., Klick Health, LifeMine Therapeutics, Mage Biologics, Merck, Mestag, Mirador Therapeutics, Mobius, Monte Rosa Tx, Morphic Therapeutics, Nexys Therapeutics, Nighthawk Therapeutics, Nimbus Therapeutics, Novartis, OncoC4, OrbiMed, Orphagen, Pendopharm, Pfizer, Protagonist,32 Bio, REDX, Roche, Roivant/Televant, Sanofi, Sobi, Sorriso, Spyre Therapeutics, Surrozen Inc., Sun Pharma, Synedgen, Takeda, Teva, Triastek, Trex Bio, TR1X Inc. TVM Lifesciences, Ventyx Biosciences, Versant Ventures, Vida Ventures, Zagbio
Speakers Bureau	AbbVie, Janssen, Takeda
Patent Holder	
Member, Scientific Advisory Board, DSMB	AbbVie, AnaptysBio, Boehringer-Ingelheim, Celgene/BMS Eli Lilly, Genentech/Roche, Janssen, Merck, MiroBio, Origo BioPharma, Pfizer, REDX Pharma, Sanofi, Takeda, Teva, Ecor1Capital, Morphic, GSK
Member, Board of Directors	
Stock Shareholder	Connect BioPharma, EnGene
Expert Testimony	Belmore Law
Other Relationship/Affiliation	Senior Scientific Director, Alimentiv Inc.

Topics to Be Discussed

- The Present -2025 a glass half full!
- Where are we headed?
  - Horizon agents
  - Combination therapy
  - Horizon indications/strategies
- Summary

IBD 2025- A glass half full!

- The introduction of multiple new treatments in the past 25 years has not resulted in consistently high rates of remission.
- Personalized medicine has not evolved as a management strategy for IBD
- We still do not understand the cause(s)



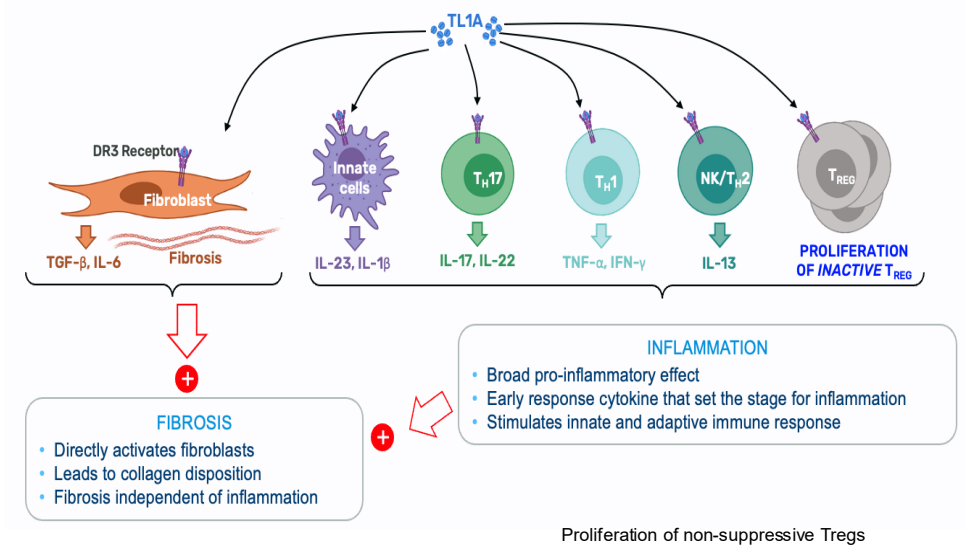
- Two emergent MOAs, anti-integrin therapy (vedolizumab) and IL-12/23 are extraordinarily safe.
- Surgical rates have fallen dramatically in both UC and CD.
- Several new MOAs have been validated

Topics to Be Discussed

- The Present = 2024 – A glass half full!
- Where are we headed?
  - Horizon agents
  - Combination therapy
  - Horizon indications/strategies
- Summary

Horizon Agents: TL1A monoclonals

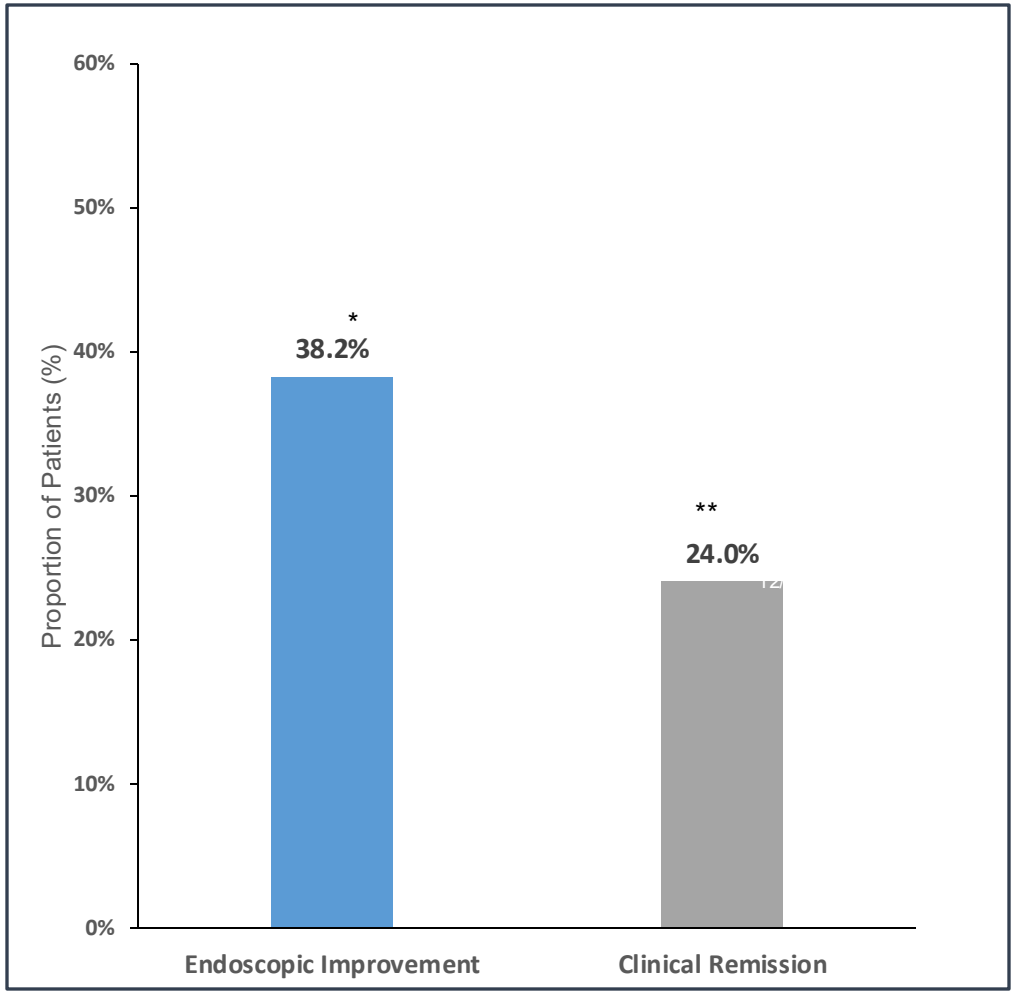
- TNF-like cytokine 1A, member of the TNF superfamily
- Variants in the TL1A-encoding gene (TNFSF15) are associated with increased IBD risk
- Expressed in antigen presenting cells, lymphocytes, and endothelial cells
- Transgenic mice develop colitis and intestinal fibrosis
- Murine anti-TL1A antibody alleviates inflammation and fibrosis



[1]Ruuls et al. Immunity 2001
[2] Yue et al. J Biol Chem 1999.
[3]Furfaro et al. Curr Drug Targets 2021.
[4]Xu et al. Front Immunol 2022.

TL1A Antagonist as Induction Therapy for UC

Endoscopic & Clinical Endpoints at Week 14



- 14 week open-label study in moderately to severely active ulcerative colitis, N=50
- propensity matched artificial control
- proof of concept achieved
- No clinically meaningful safety signal observed

Adapted from ECCO'20 Vienna Congress Presentation – Speaker: Dr. Silvio Danese. Danese et al. Safety, Tolerability and efficacy of anti-TL1A antibody PF-06480605 in treatment of ulcerative colitis: the open-label, multicentre, Phase 2a TUSCANY study.

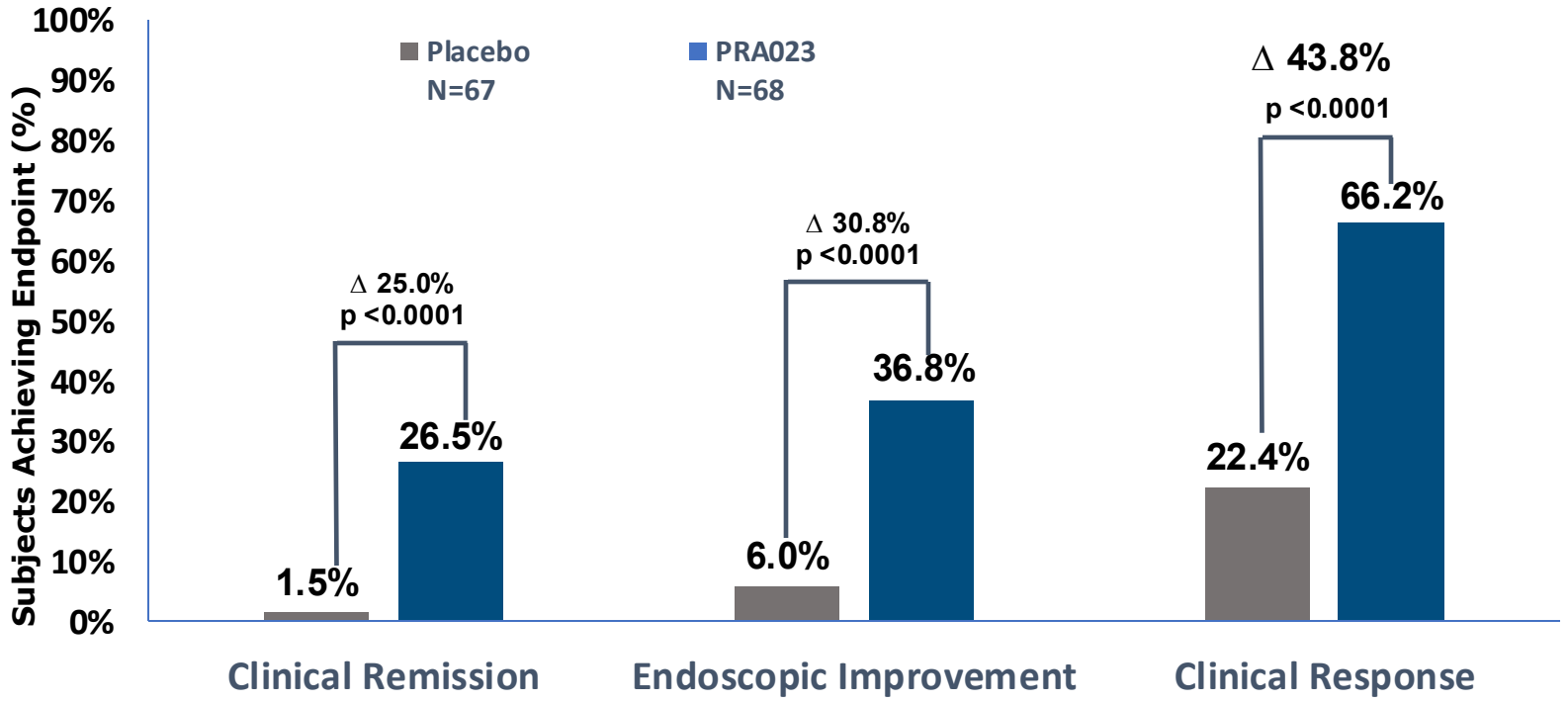
Primary and Secondary Endpoints at Week 12 Tulisokibart vs. Placebo

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Anti-TL1A Monoclonal Antibody Tulisokibart for Ulcerative Colitis

Bruce E. Sands, M.D., Brian G. Feagan, M.D., Laurent Peyrin-Biroulet, M.D., Ph.D., Silvio Danese, M.D., David T. Rubin, M.D., Olivier Laurent, Ph.D., Allison Luo, M.D., Deanna D. Nguyen, M.D., Jiandong Lu, Ph.D., Mark Yen, M.D., Jaroslaw Leszczyszyn, M.D., Ph.D., Radosław Kempiński, M.D., Ph.D., Dermot P.B. McGovern, M.D., Ph.D., Christopher Ma, M.D., Timothy E. Ritter, M.D., and Stephan Targan, M.D., for the ARTEMIS-UC Study Group*

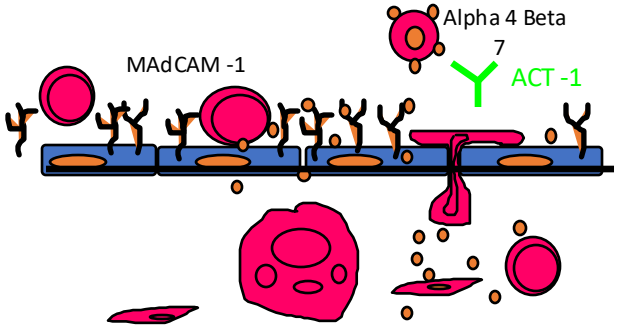


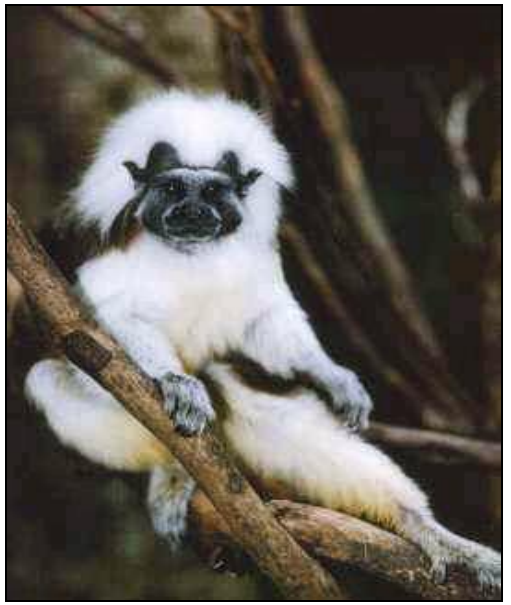
Clinical remission per mMS is defined as endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1 and not greater than Baseline; Endoscopic improvement is defined as endoscopy subscore ≤ 1 with no friability; Clinical response per mMS is defined as reduction from Baseline ≥ 2 points and ≥ 30% in 3-component Modified Mayo Score, accompanied by a reduction ≥ 1 in rectal bleeding subscore or absolute rectal bleeding subscore ≤ 1. | P-values for testing the treatment difference are based on Cochran-Mantel-Haenszel test adjusted for prior biologic exposure status and CDx status. All endpoints are statistically significant according to multiplicity controlled 2-sided alpha of 0.05.

Sands BE. Et al. New Eng J Med. 2024;391(12):1119-29

Oral Alpha 4 Beta7 Blockade: Background

- Ligand for $\alpha_4\beta_7$ is MAdCAM
- Animal models show that ACT-1 selectively blocks trafficking of $\alpha_4\beta_7$ positive lymphocytes to the gut
- Raises possibility of gut specific immune modulation
- Striking benefit in cotton-top tamarin model





Hesterberg PE et al. Gastroenterology 1996;111:1373-80
Podolsky et al. JCI 1993;92:372-80

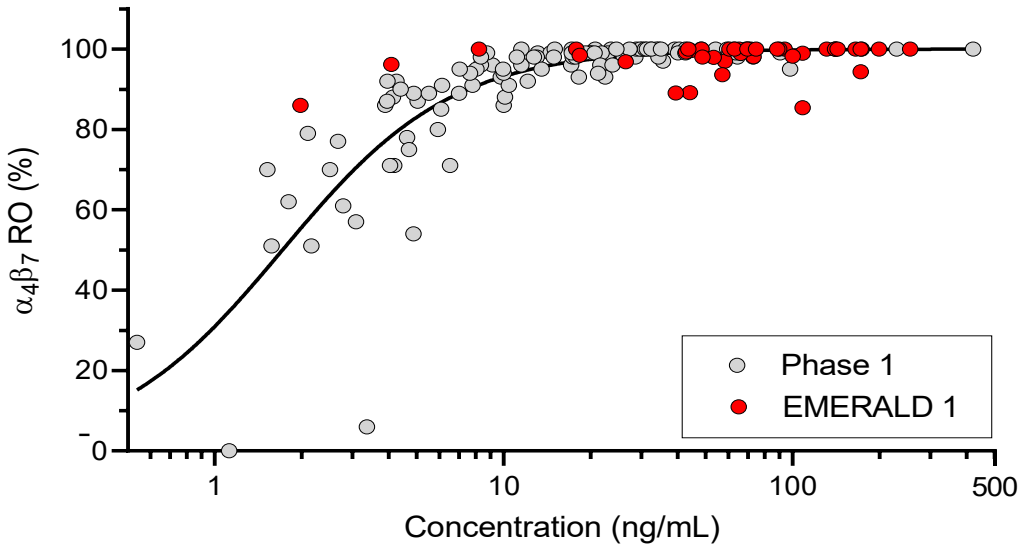
Oral Alpha4 Beta7 Antagonists

- Highly successful MOA
- Vedolizumab market leader in UC
- Multiple new indications (pouchitis, post-operative CD, GVH)
- Potential in combination therapy = the “polypill”

Morphic Data: Patient a4β7 Receptor Occupancy (RO) Consistent with Healthy Volunteer RO

a4β7 selectivity over a4β1 consistent with Phase 1 results

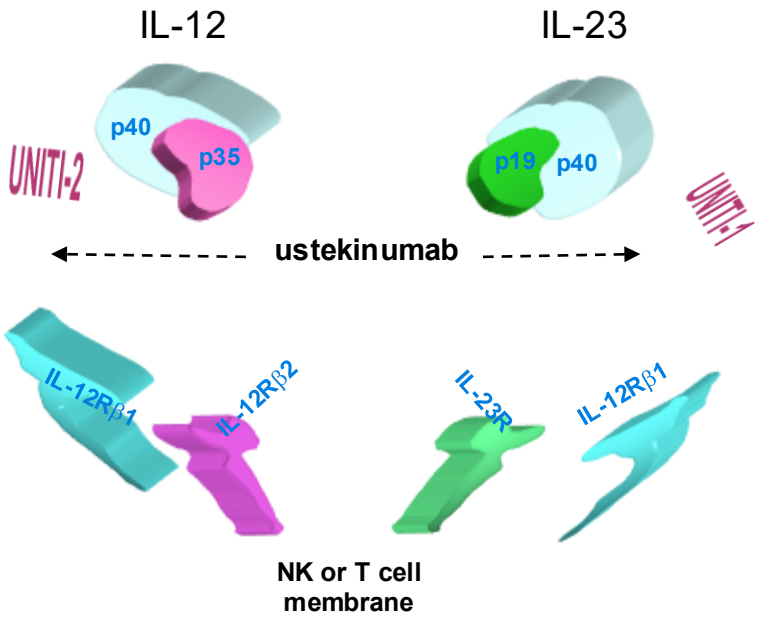
- a4β7 RO achieved early and sustained saturating levels
- a4β1 RO remained at low levels
- No lymphocytosis or changes to circulating naïve T-cells were observed
- a4β1 projected RO was below the limit of quantitation with mean trough value estimated to be <15%



RO: Receptor Occupancy; BLQ, Below Limit of Quantification

UEGW Congress Abstract 2024

Anti-p40 Ustekinumab: Background for Oral Il-23



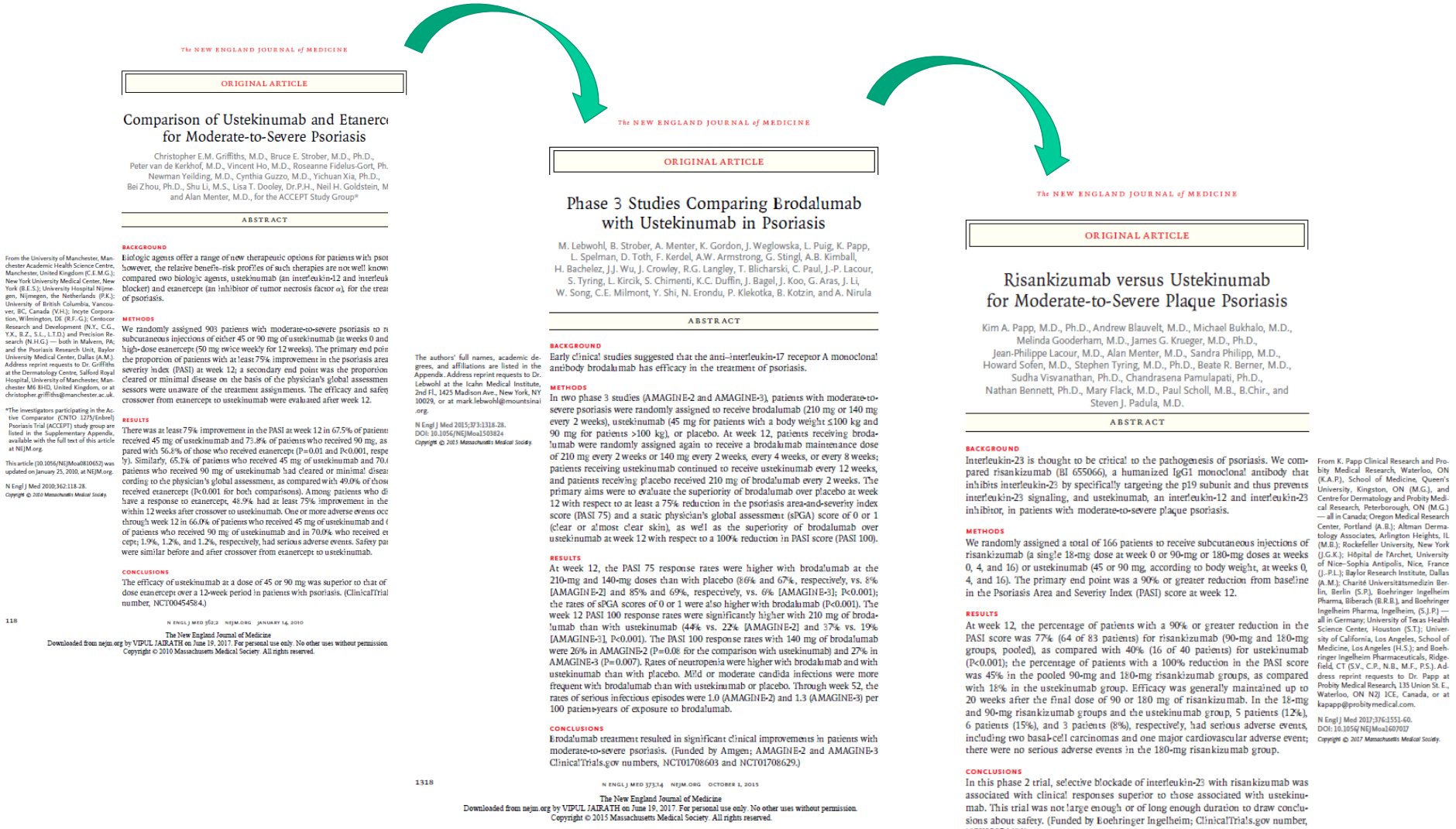
No IL-12 or IL-23 intracellular signal

- IL-12 & IL-23 are key cytokines in the pathogenic immune cascade of Crohn's disease
- Ustekinumab is a fully human IgG1k monoclonal antibody binding the **p40 subunit** of interleukin-12 and -23
- Inhibits IL-12- and IL-23-mediated signaling, cellular activation, and downstream cytokine production
- Approved for moderate to severe psoriasis and psoriatic arthritis
- Induction efficacy recently demonstrated in a broad CD population in UNITI-1[1] and UNITI-2[2]

[1] *Sandborn W, et al. Oral presentation. CCFA 2015 and Rutgeerts P, et al . Oral presentation. ECCO 2016.*
[2] *Feagan B, et al. Oral presentation. ACG and UEGW 2015.*

Sandborn W.J., et al. DDW 2016. Presentation 768.

Transformational Efficacy in Psoriasis Therapy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Ustekinumab and Etanerc for Moderate-to-Severe Psoriasis

Christopher E.M. Griffiths, M.D., Bruce E. Strober, M.D., Ph.D., Peter van de Kerkhof, M.D., Vincent Ho, M.D., Roseanne Fidelus-Gort, Ph. Newman Yeilding, M.D., Cynthia Guzzo, M.D., Yichuan Xia, Ph.D., Bei Zhou, Ph.D., Shu Li, M.S., Lisa T. Dooley, Dr.P.H., Neil H. Goldstein, M and Alan Menter, M.D., for the ACCEPT Study Group*

ABSTRACT

BACKGROUND

Biologic agents offer a range of new therapeutic options for patients with psor however, the relative benefit–risk profiles of such therapies are not well known compared two biologic agents, ustekinumab (an interleukin-12 and interleuk blocker) and etanercept (an inhibitor of tumor necrosis factor α), for the treat of psoriasis.

METHODS

We randomly assigned 903 patients with moderate-to-severe psoriasis to r subcutaneous injections of either 45 or 90 mg of ustekinumab (at weeks 0 and high-dose etanercept (50 mg twice weekly for 12 weeks). The primary end poin the proportion of patients with at least 75% improvement in the psoriasis area severity index (PASI) at week 12; a secondary end point was the proportion cleared or minimal disease on the basis of the physician's global assessmen sessors were unaware of the treatment assignments. The efficacy and safety crossover from etanercept to ustekinumab were evaluated after week 12.

RESULTS

There was at least 75% improvement in the PASI at week 12 in 67.5% of patient received 45 mg of ustekinumab and 73.8% of patients who received 90 mg, as pared with 56.8% of those who received etanercept (P=0.01 and P<0.001, respe ly). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.4 patients who received 90 mg of ustekinumab had cleared or minimal disea cording to the physician's global assessment, as compared with 49.0% of those received etanercept (P<0.001 for both comparisons). Among patients who di have a response to etanercept, 48.9% had at least 75% improvement in the within 12 weeks after crossover to ustekinumab. One or more adverse events occ through week 12 in 66.0% of patients who received 45 mg of ustekinumab and of patients who received 90 mg of ustekinumab and in 70.0% who received et cept; 1.9%, 1.2%, and 1.2%, respectively, had serious adverse events. Safety pat were similar before and after crossover from etanercept to ustekinumab.

CONCLUSIONS

The efficacy of ustekinumab at a dose of 45 or 90 mg was superior to that of dose etanercept over a 12-week period in patients with psoriasis. (ClinicalTrial number, NCT00454584.)

From the University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom (C.E.M.G.); New York University Medical Center, New York (B.E.S.); University Hospital Nijmegen, Nijmegen, the Netherlands (P.K.); University of British Columbia, Vancouver, BC, Canada (V.H.); Incyte Corporation, Wilmington, DE (R.F.-G.); Centocor Research and Development (N.Y., C.G., Y.X., B.Z., S.L., L.T.D.) and Precision Research (N.H.G.) — both in Malvern, PA; and the Psoriasis Research Unit, Baylor University Medical Center, Dallas (A.M.). Address reprint requests to Dr. Griffiths at the Dermatology Centre, Salford Royal Hospital, University of Manchester, Manchester M6 8HD, United Kingdom, or at christopher.griffiths@manchester.ac.uk.

*The investigators participating in the Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial (ACCEPT) study group are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

This article (10.1056/NEJMoa0810652) was updated on January 25, 2010, at NEJM.org.

N Engl J Med 2010;362:118-28.

Copyright © 2010 Massachusetts Medical Society.

118

N ENGL J MED 362;2 NEJM.ORG JANUARY 14, 2010

The New England Journal of Medicine

Downloaded from nejm.org by VIPUL JAIRATH on June 19, 2017. For personal use only. No other uses without permission.

Copyright © 2010 Massachusetts Medical Society. All rights reserved.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis

M. Lebwohl, B. Strober, A. Menter, K. Gordon, J. Weglowska, L. Puig, K. Papp, L. Spelman, D. Toth, F. Kerdel, A.W. Armstrong, G. Stingl, A.B. Kimball, H. Bachelez, J.J. Wu, J. Crowley, R.G. Langley, T. Blicharski, C. Paul, J.-P. Lacour, S. Tyring, L. Kircik, S. Chimenti, K.C. Duffin, J. Bagel, J. Koo, G. Aras, J. Li, W. Song, C.E. Milmont, Y. Shi, N. Erondu, P. Klekotka, B. Kotzin, and A. Nirula

ABSTRACT

BACKGROUND

Early clinical studies suggested that the anti–interleukin-17 receptor A monoclonal antibody brodalumab has efficacy in the treatment of psoriasis.

METHODS

In two phase 3 studies (AMAGINE-2 and AMAGINE-3), patients with moderate-to-severe psoriasis were randomly assigned to receive brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg), or placebo. At week 12, patients receiving brodalumab were randomly assigned again to receive a brodalumab maintenance dose of 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks, or every 8 weeks; patients receiving ustekinumab continued to receive ustekinumab every 12 weeks, and patients receiving placebo received 210 mg of brodalumab every 2 weeks. The primary aims were to evaluate the superiority of brodalumab over placebo at week 12 with respect to at least a 75% reduction in the psoriasis area-and-severity index score (PASI 75) and a static physician's global assessment (sPGA) score of 0 or 1 (clear or almost clear skin), as well as the superiority of brodalumab over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100).

RESULTS

At week 12, the PASI 75 response rates were higher with brodalumab at the 210-mg and 140-mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively, vs. 6% [AMAGINE-3]; P<0.001); the rates of sPGA scores of 0 or 1 were also higher with brodalumab (P<0.001). The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (P=0.08 for the comparison with ustekinumab) and 27% in AMAGINE-3 (P=0.007). Rates of neutropenia were higher with brodalumab and with ustekinumab than with placebo. Mild or moderate candida infections were more frequent with brodalumab than with ustekinumab or placebo. Through week 52, the rates of serious infectious episodes were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumab.

CONCLUSIONS

Brodalumab treatment resulted in significant clinical improvements in patients with moderate-to-severe psoriasis. (Funded by Amgen; AMAGINE-2 and AMAGINE-3 ClinicalTrials.gov numbers, NCT01708603 and NCT01708629.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Lebwohl at the Icahn Medical Institute, 2nd Fl., 1425 Madison Ave., New York, NY 10029, or at mark.lebwohl@mountsinai.org.

N Engl J Med 2015;373:1318-28.

DOI: 10.1056/NEJMoa1503824

Copyright © 2015 Massachusetts Medical Society.

1318

N ENGL J MED 373;14 NEJM.ORG OCTOBER 1, 2015

The New England Journal of Medicine

Downloaded from nejm.org by VIPUL JAIRATH on June 19, 2017. For personal use only. No other uses without permission.

Copyright © 2015 Massachusetts Medical Society. All rights reserved.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis

Kim A. Papp, M.D., Ph.D., Andrew Blauvelt, M.D., Michael Bukhalo, M.D., Melinda Gooderham, M.D., James G. Krueger, M.D., Ph.D., Jean-Philippe Lacour, M.D., Alan Menter, M.D., Sandra Philipp, M.D., Howard Sofen, M.D., Stephen Tyring, M.D., Ph.D., Beate R. Berner, M.D., Sudha Visvanathan, Ph.D., Chandrasena Pamulapati, Ph.D., Nathan Bennett, Ph.D., Mary Flack, M.D., Paul Scholl, M.B., B.Chir., and Steven J. Padula, M.D.

ABSTRACT

BACKGROUND

Interleukin-23 is thought to be critical to the pathogenesis of psoriasis. We compared risankizumab (BI 655066), a humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specifically targeting the p19 subunit and thus prevents interleukin-23 signaling, and ustekinumab, an interleukin-12 and interleukin-23 inhibitor, in patients with moderate-to-severe plaque psoriasis.

METHODS

We randomly assigned a total of 166 patients to receive subcutaneous injections of risankizumab (a single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg, according to body weight, at weeks 0, 4, and 16). The primary end point was a 90% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12.

RESULTS

At week 12, the percentage of patients with a 90% or greater reduction in the PASI score was 77% (64 of 83 patients) for risankizumab (90-mg and 180-mg groups, pooled), as compared with 40% (16 of 40 patients) for ustekinumab (P<0.001); the percentage of patients with a 100% reduction in the PASI score was 45% in the pooled 90-mg and 180-mg risankizumab groups, as compared with 18% in the ustekinumab group. Efficacy was generally maintained up to 20 weeks after the final dose of 90 or 180 mg of risankizumab. In the 18-mg and 90-mg risankizumab groups and the ustekinumab group, 5 patients (12%), 6 patients (15%), and 3 patients (8%), respectively, had serious adverse events, including two basal-cell carcinomas and one major cardiovascular adverse event; there were no serious adverse events in the 180-mg risankizumab group.

CONCLUSIONS

In this phase 2 trial, selective blockade of interleukin-23 with risankizumab was associated with clinical responses superior to those associated with ustekinumab. This trial was not large enough or of long enough duration to draw conclusions about safety. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT02054481.)

From K. Papp Clinical Research and Probity Medical Research, Waterloo, ON (K.A.P.), School of Medicine, Queen's University, Kingston, ON (M.G.), and Centre for Dermatology and Probity Medical Research, Peterborough, ON (M.G.) — all in Canada; Oregon Medical Research Center, Portland (A.B.); Altman Dermatology Associates, Arlington Heights, IL (M.B.); Rockefeller University, New York (J.G.K.); Hôpital de l'Archet, University of Nice–Sophia Antipolis, Nice, France (J.-P.L.); Baylor Research Institute, Dallas (A.M.); Charité Universitätsmedizin Berlin, Berlin (S.P.), Boehringer Ingelheim Pharma, Biberach (B.R.B.), and Boehringer Ingelheim Pharma, Ingelheim, (S.J.P.) — all in Germany; University of Texas Health Science Center, Houston (S.T.); University of California, Los Angeles, School of Medicine, Los Angeles (H.S.); and Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (S.V., C.P., N.B., M.F., P.S.). Address reprint requests to Dr. Papp at Probity Medical Research, 135 Union St. E., Waterloo, ON N2J 1C8, Canada, or at kapapp@probity-medical.com.

N Engl J Med 2017;376:1551-60.

DOI: 10.1056/NEJMoa1607017

Copyright © 2017 Massachusetts Medical Society.

N ENGL J MED 376;16 NEJM.ORG APRIL 20, 2017

1551

The New England Journal of Medicine

Downloaded from nejm.org by VIPUL JAIRATH on June 19, 2017. For personal use only. No other uses without permission.

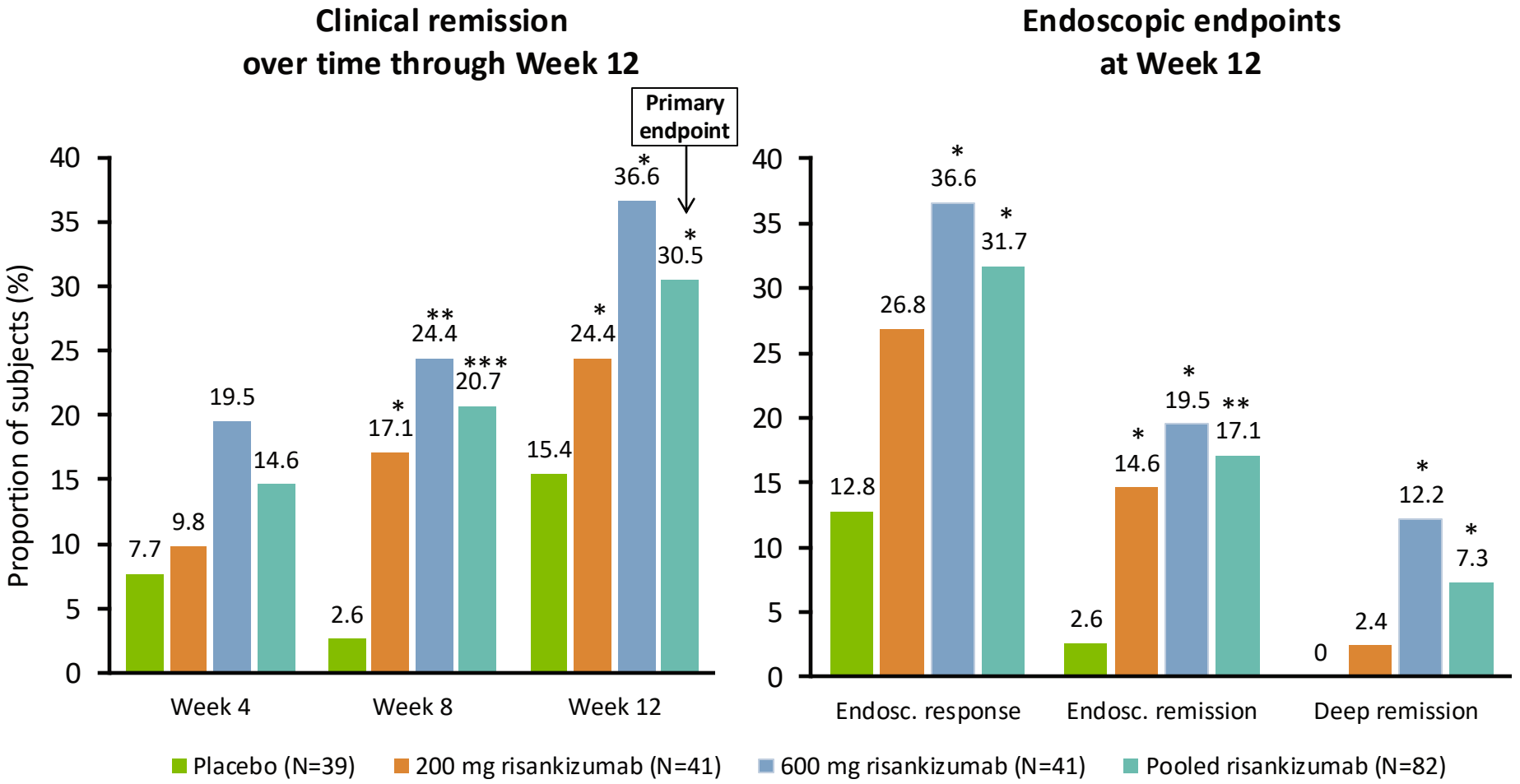
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Griffiths CE. et al. N Eng J Med. 2010;362(2):118-28

Lebwohl M et al. N Eng J Med. 2015;373(14):1318-28.

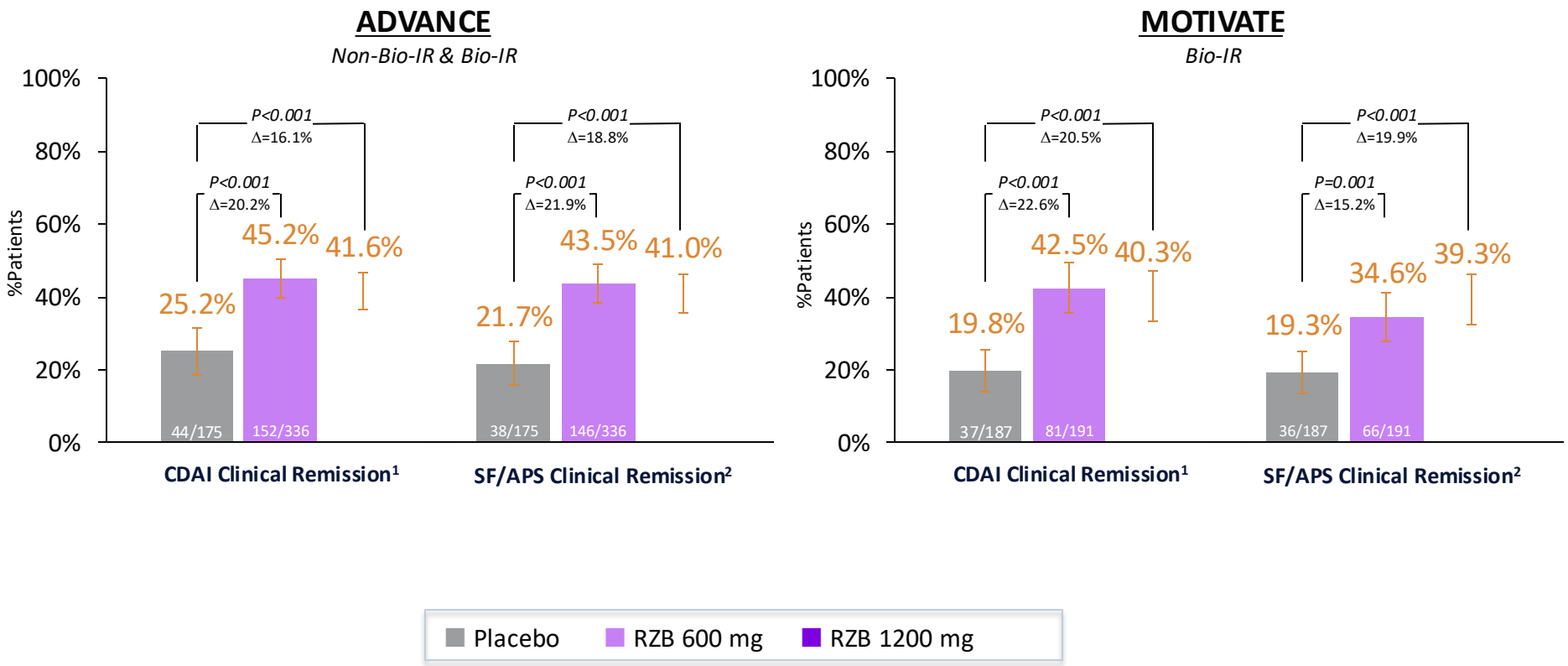
Papp KA, et al. N Eng J Med. 2017;376(16):1551-1560.

Risankizumab for CD: Is anti-P19 the Answer?



Feagan B, et al. Lancet 2017;389:1699–1709

Risankizumab Induction: Clinical Remission Week 12



Ferrante et al UEGW 2021

Oral IL-23 Peptide Therapy for Psoriasis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Oral Interleukin-23–Receptor Antagonist Peptide for Plaque Psoriasis

Robert Bissonnette, M.D., Andreas Pinter, M.D., Laura K. Ferris, M.D., Ph.D., Sascha Gerdes, M.D., Phoebe Rich, M.D., Ronald Vender, M.D., Megan Miller, M.P.H., Yaung-Kaung Shen, Ph.D., Arun Kannan, Ph.D., Shu Li, Ph.D., Cynthia DeKlotz, M.D., and Kim Papp, M.D., Ph.D.

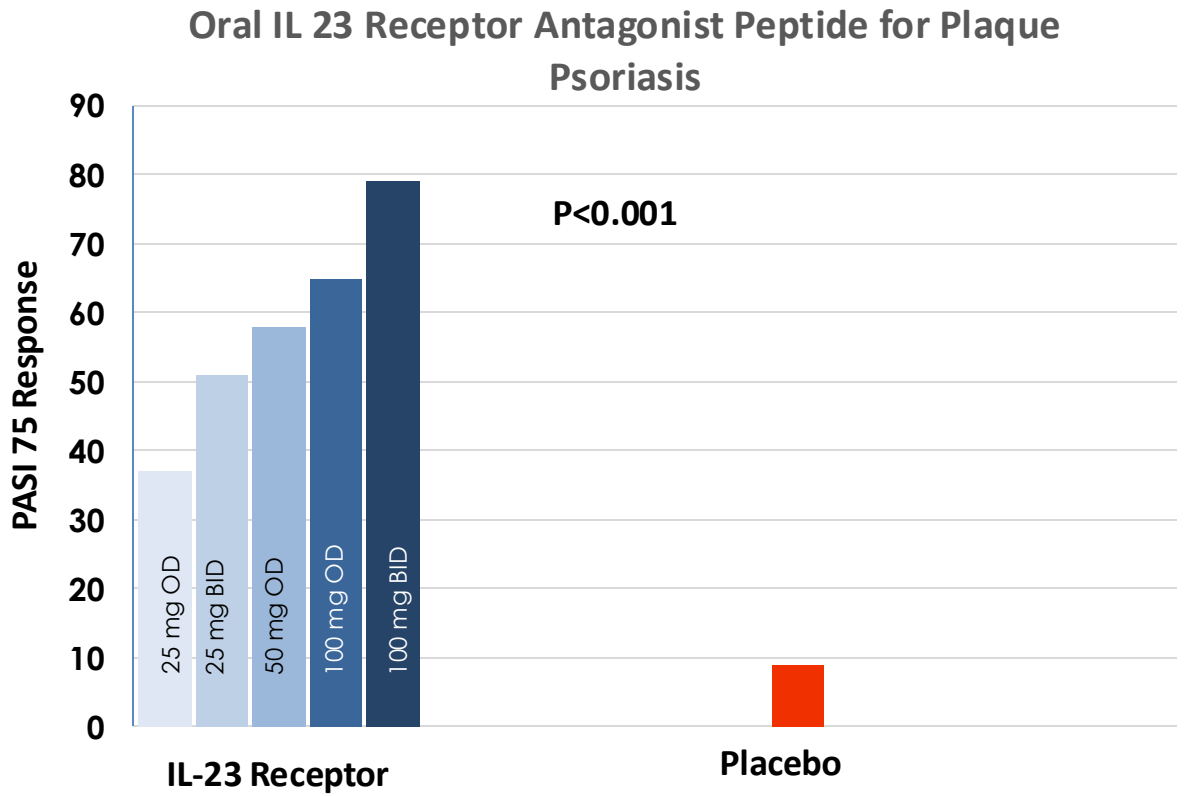
ABSTRACT

BACKGROUND
The use of monoclonal antibodies has changed the treatment of several immune-mediated inflammatory diseases, including psoriasis. However, these large proteins must be administered by injection. JNJ-77242113 is a novel, orally administered interleukin-23–receptor antagonist peptide that selectively blocks interleukin-23 signaling and downstream cytokine production.

METHODS
In this phase 2 dose-finding trial, we randomly assigned patients with moderate-to-severe plaque psoriasis to receive JNJ-77242113 at a dose of 25 mg once daily, 25 mg twice daily, 50 mg once daily, 100 mg once daily, or 100 mg twice daily or placebo for 16 weeks. The primary end point was a reduction from baseline of at least 75% in the Psoriasis Area and Severity Index (PASI) score (PASI 75 response; PASI scores range from 0 to 72, with higher scores indicating greater extent or severity of psoriasis) at week 16.

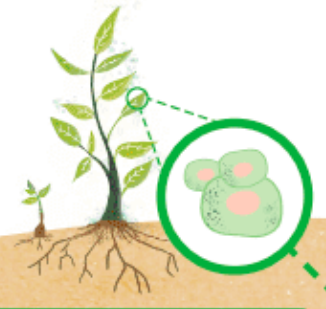
RESULTS
A total of 255 patients underwent randomization. The mean PASI score at baseline was 19.1. The mean duration of psoriasis was 18.2 years, and 78% of the patients across all the trial groups had previously received systemic treatments. At week 16, the percentages of patients with a PASI 75 response were higher among those in the JNJ-77242113 groups (37%, 51%, 58%, 65%, and 79% in the 25-mg once-daily, 25-mg twice-daily, 50-mg once-daily, 100-mg once-daily, and 100-mg twice-daily groups, respectively) than among those in the placebo group (9%), a finding that showed a significant dose–response relationship (P<0.001). The most common adverse events included coronavirus disease 2019 (in 12% of the patients in the placebo group and in 11% of those across the JNJ-77242113 dose groups) and nasopharyngitis (in 5% and 7%, respectively). The percentages of patients who had at least one adverse event were similar in the combined JNJ-77242113 dose group (52%) and the placebo group (51%). There was no evidence of a dose-related increase in adverse events across the JNJ-77242113 dose groups.

CONCLUSIONS
After 16 weeks of once- or twice-daily oral administration, treatment with the interleukin-23–receptor antagonist peptide JNJ-77242113 showed greater efficacy than placebo in patients with moderate-to-severe plaque psoriasis. (Funded by Janssen Research and Development; FRONTIER 1 ClinicalTrials.gov number, NCT05223868.)



UNDERSTANDING RNAi

RNAi, or "RNA Interference," is a natural process that occurs in the cells of plants, animals, and people.

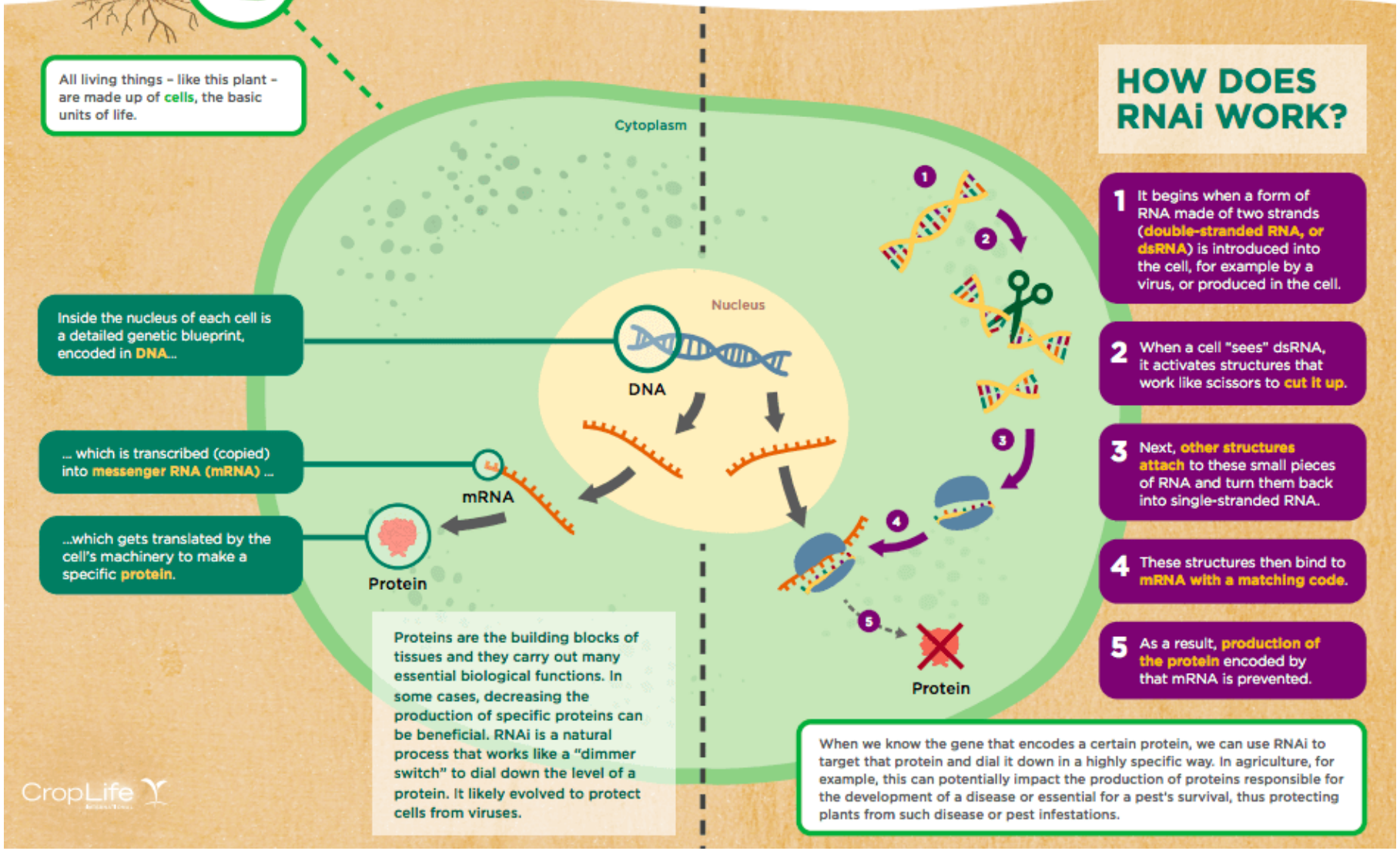


All living things – like this plant – are made up of **cells**, the basic units of life.

Inside the nucleus of each cell is a detailed genetic blueprint, encoded in **DNA**...

... which is transcribed (copied) into **messenger RNA (mRNA)** ...

...which gets translated by the cell's machinery to make a specific **protein**.



Proteins are the building blocks of tissues and they carry out many essential biological functions. In some cases, decreasing the production of specific proteins can be beneficial. RNAi is a natural process that works like a "dimmer switch" to dial down the level of a protein. It likely evolved to protect cells from viruses.

HOW DOES RNAi WORK?

1. It begins when a form of RNA made of two strands (**double-stranded RNA, or dsRNA**) is introduced into the cell, for example by a virus, or produced in the cell.
2. When a cell "sees" dsRNA, it activates structures that work like scissors to **cut it up**.
3. Next, **other structures attach** to these small pieces of RNA and turn them back into single-stranded RNA.
4. These structures then bind to **mRNA with a matching code**.
5. As a result, **production of the protein** encoded by that mRNA is prevented.

When we know the gene that encodes a certain protein, we can use RNAi to target that protein and dial it down in a highly specific way. In agriculture, for example, this can potentially impact the production of proteins responsible for the development of a disease or essential for a pest's survival, thus protecting plants from such disease or pest infestations.

CropLife

Obefazimod Induction Therapy for UC

- Oral, small molecule agonist that stimulates sRNA production
- Inhibits pro-inflammatory cytokine production
- Excellent safety profile in HIV therapy studies
- Previous positive 2a POC
- Phase 2 study in UC

Articles

ABX464 (obefazimod) for moderate-to-severe, active ulcerative colitis: a phase 2b, double-blind, randomised, placebo-controlled induction trial and 48 week, open-label extension

Severine Vermeire*, Bruce E Sands*, Herbert Tilg, Zsolt Tulassay, Radoslaw Kempinski, Silvio Danese, Ivan Bunganič, Josianne Nitcheu, Julien Santo, Didier Scherrer, Sophie Biguenet, Hartmut J Ehrlich, Jean-Marc Steens, Paul Gineste, William J Sandborn

Lancet Gastroenterol Hepatol 2022; 7: 1024–35

Published Online September 5, 2022 https://doi.org/10.1016/S2468-1253(22)00233-3

See Comment page 977

*Contributed equally

Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium (Prof S Vermeire MD); Dr Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Prof B E Sands MD); Department of Internal Medicine, Division of Gastroenterology, Hepatology and Endocrinology and Metabolism, Medical University of Innsbruck, Innsbruck, Austria (Prof H Tilg MD); Department of Internal Medicine, Semmelweis University, Budapest, Hungary (Z Tulassay MD); Department of Gastroenterology and Hepatology, Wroclaw Medical University, Wroclaw, Poland (R Kempinski MD); Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele, University Vita-Salute San Raffaele, Milano, Italy (Prof S Danese MD); Department of Gastroenterology, Gastro hm, Prešov, Slovakia (I Bunganič MD); Abivax, Paris, France (J Nitcheu PhD, J Santo PhD, D Scherrer PhD, S Biguenet MD, H J Ehrlich MD, J-M Steens MD, P Gineste PharmD); Division of Gastroenterology, University of California San Diego, La Jolla, CA, USA (Prof W J Sandborn MD)

Summary

Background ABX464 (obefazimod) is a small molecule that selectively upregulates miR-124 in immune cells. We aimed to assess ABX464 as a treatment for patients with moderate-to-severe, active ulcerative colitis.

Methods In this phase 2b, double-blind, randomised, placebo-controlled induction trial, patients were recruited from 95 centres (hospitals and health-care centres) in 16 countries. Eligible patients were aged 18–75 years, with a diagnosis of moderate-to-severe, active ulcerative colitis and a modified Mayo Score (MMS) of 5 points or higher, and a documented non-response or intolerance to previous treatment. Enrolled patients were randomly assigned (1:1:1:1) via an interactive voice and web response system to receive once daily oral ABX464 100 mg, ABX464 50 mg, ABX464 25 mg, or matched placebo. Randomisation was stratified according to study site (US *vs* non-US) and to whether the patient had previous exposure to second-line treatment with biologics or JAK inhibitors. The primary endpoint was the change from baseline in MMS at week 8. The primary efficacy analysis was done in the full analysis set (FAS), defined as all randomly assigned patients who received at least one dose of study treatment and had baseline data for at least one efficacy variable, and was analysed according to the principles of intention-to-treat. Safety analyses included patients who had been randomly assigned and who received at least one dose of study treatment. The 96 week open-label extension is ongoing. This study is registered with ClinicalTrials.gov, NCT04023396.

Findings Between Aug 13, 2019, and April 16, 2021, 254 patients were randomly allocated to ABX464 100 mg (n=64), ABX464 50 mg (n=63), ABX464 25 mg (n=63), or placebo (n=64). Two patients, both in the ABX464 25 mg group, were excluded from the FAS. In the FAS at week 8, the least squares mean (LSM) change from baseline in MMS was −2·9 (95% CI −3·4 to −2·5) for the ABX464 100 mg group, −3·2 (−3·7 to −2·7) for the ABX464 50 mg group, −3·1 (−3·6 to −2·6) for the ABX464 25 mg group, and −1·9 (−2·4 to −1·5) for placebo group; the magnitude of the difference in MMS from baseline was significantly greater in all three ABX464 groups compared with placebo (p=0·0039 for ABX464 100 mg *vs* placebo, p=0·0003 for ABX464 50 mg *vs* placebo, and p=0·0010 for ABX464 25 mg *vs* placebo). The most frequently reported adverse event was headache, which was reported for 27 (42%) of 64 patients in the ABX464 100 mg group, 19 (30%) of 63 in the 50 mg group, 13 (21%) of 62 in the 25 mg group, and five (8%) of 64 in the placebo group. Severe (grade 3) headache was reported for three (5%) patients in the ABX464 group 100 mg group, two (3%) in the ABX464 50 mg group, one (2%) in the ABX464 25 mg group, and none in the placebo group. The only serious adverse event reported for two or more patients in any group was ulcerative colitis (one in each of the ABX464 100 mg and 50 mg groups, and three [5%] in the placebo group).

Interpretation All doses of ABX464 significantly improved moderate-to-severe, active ulcerative colitis compared with placebo, as measured by changes in MMS from baseline to week 8. A phase 3 clinical programme is ongoing.

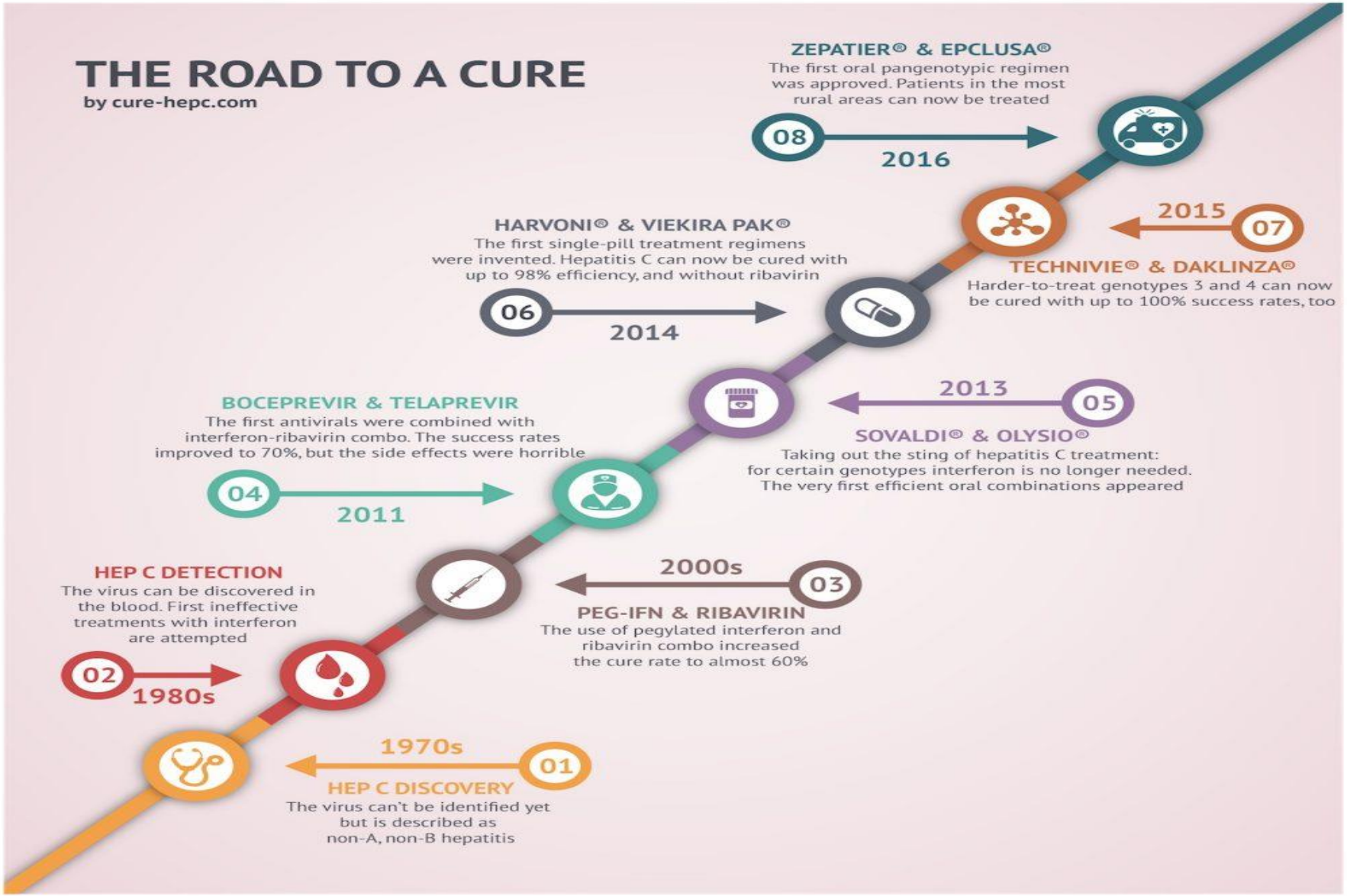
Funding Abivax.

Introduction

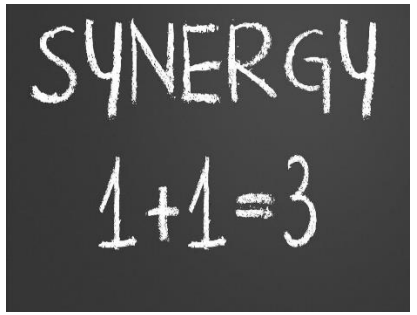
Ulcerative colitis is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which starts in the rectum and extends proximally in a continuous manner through part of the colon or the entire colon.[1] Bloody diarrhoea is the characteristic symptom of the disease. The choice of treatment for ulcerative colitis is generally based on the pattern of involvement of the disease and the degree of clinical activity.[2] In uncomplicated disease (eg, amenable to first-line treatment), 5-aminosalicylic acids (5-ASA), administered orally or rectally, is usually sufficient for inducing and sustaining remission. In patients with moderate-to-severe ulcerative colitis not responding to 5-ASA, additional therapy such as

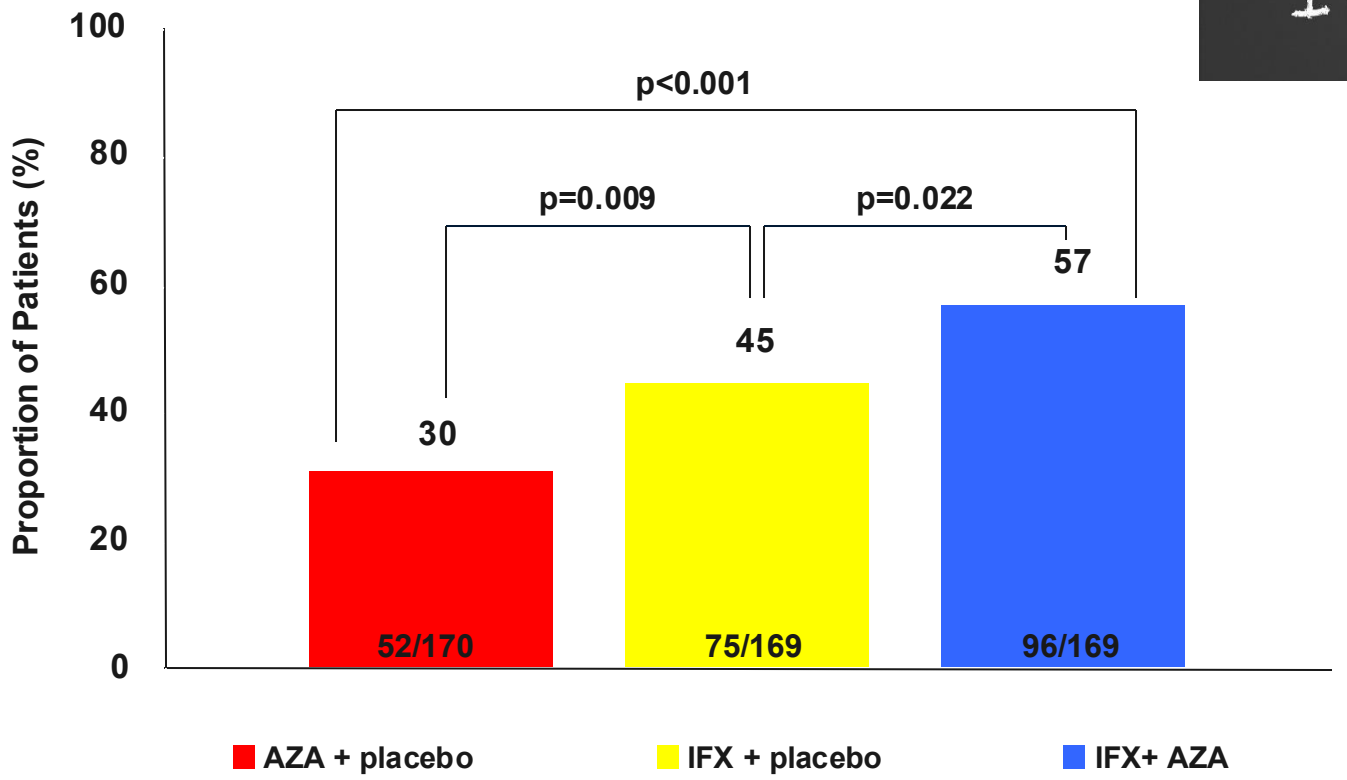
Vermiere S. et al. Lancet Gastro Hepatology. Sept 2022

Combination Therapy….
Behold HCV treatment



SONIC Provides a Clue!





Colombel JF. et al. N Engl J Med. 2010 Apr 15;362(15):1383-95.

Combination Therapy VEGA: Guselkumab + Golimumab in UC

STUDY

- Phase 2a, randomized, double-blind, placebo-controlled, active-comparator-controlled, parallel-group, proof-of-concept, multicentre study

PURPOSE

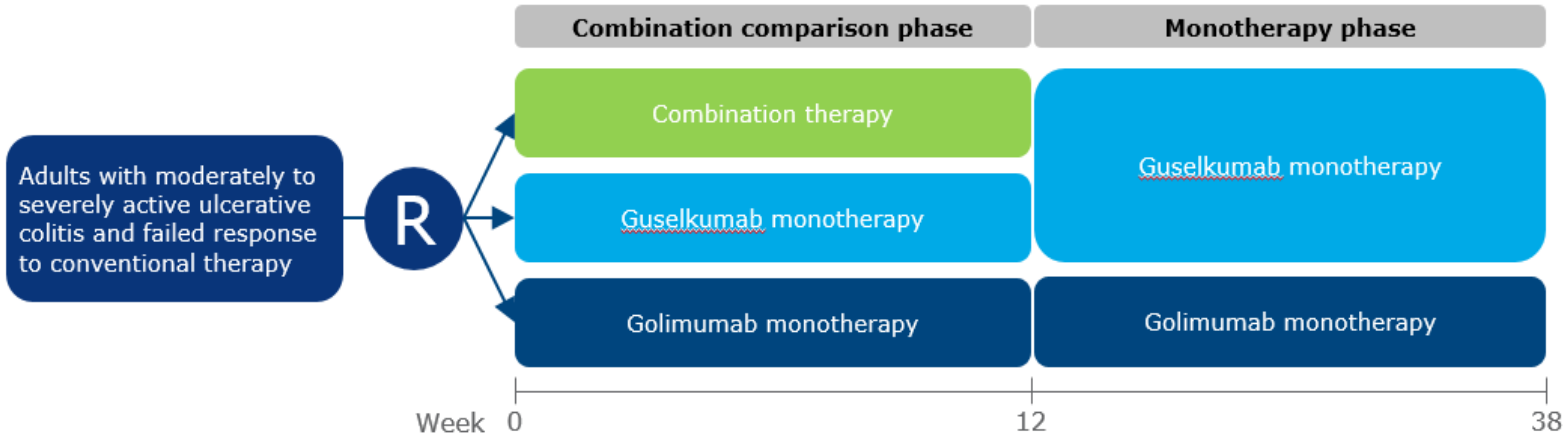
- To evaluate the safety and efficacy of combination therapy with guselkumab and golimumab in patients with moderately to severely active ulcerative colitis

PRIMARY ENDPOINT

- Clinical response at Week 12 defined by Mayo score

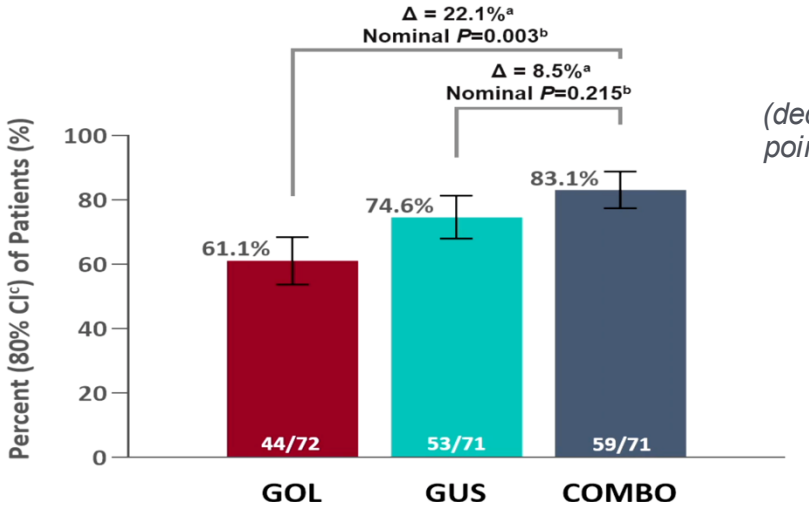
MAJOR SECONDARY ENDPOINTS

- Clinical remission at Week 12 defined by Mayo score



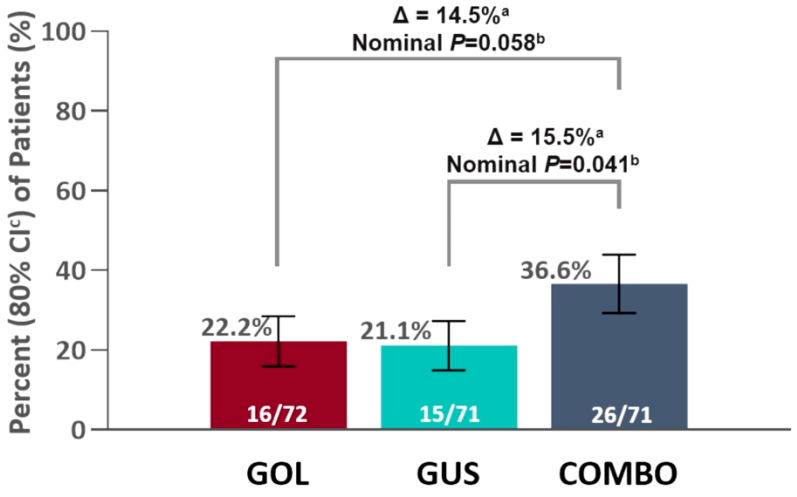
Feagan BG et al. Lancet Gastroenterol Hepatol.2023;8(4):307-320.

Clinical Response and Remission at Week 12

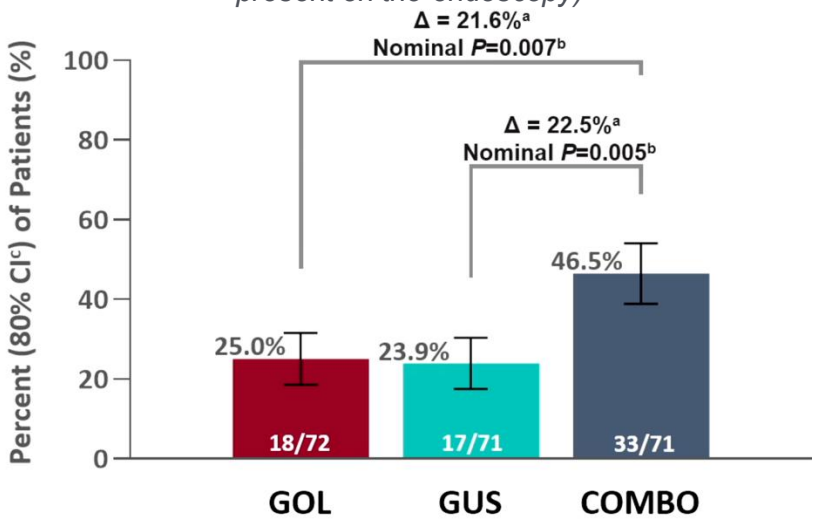


Clinical Response
(decrease from baseline in the Mayo score ≥30% and ≥3 points with either a decrease in rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1)

Clinical Remission
(Mayo score ≤2 with no individual subscore >1



Clinical Remission
(modified Mayo score: Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy)



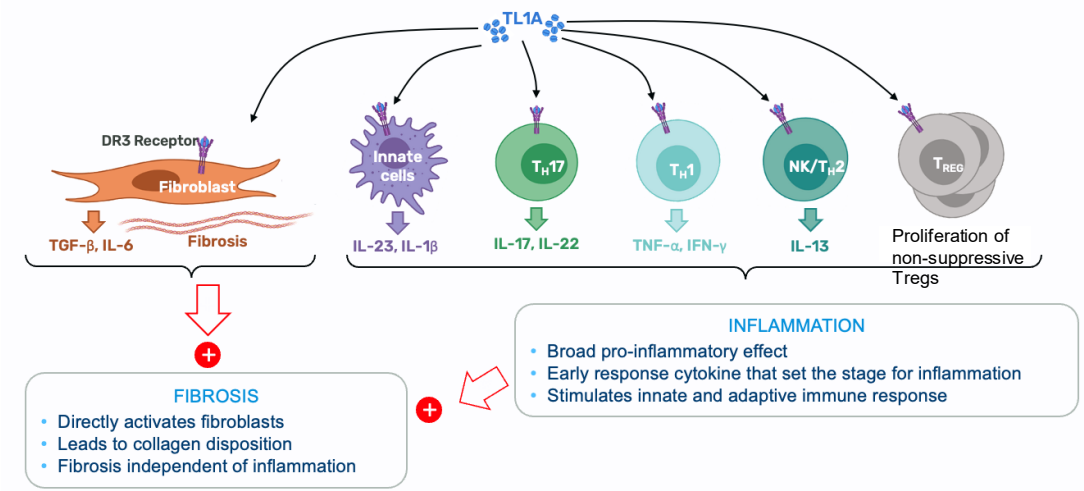
ECCO 2022 data may include drugs, doses and indications not approved by Health Canada

Sands BE, Feagan BG, Sandborn WJ, et al. Efficacy and safety of combination induction therapy with guselkumab and golimumab in participants with moderately-to-severely active Ulcerative Colitis: Results through week 12 of a phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept study (OP36). J Crohn's Colitis 2022;16(S1);i042.

TL1A: First IBD Target That Mediates Inflammation & Fibrosis

- TNF-like cytokine 1A, member of the TNF superfamily[1,2]
- Expressed in antigen presenting cells, lymphocytes, and endothelial cells.
- Since its first discovery in 2001 delete, TL1A has been linked to multiple autoinflammatory & fibrotic diseases, including IBD[3,4]

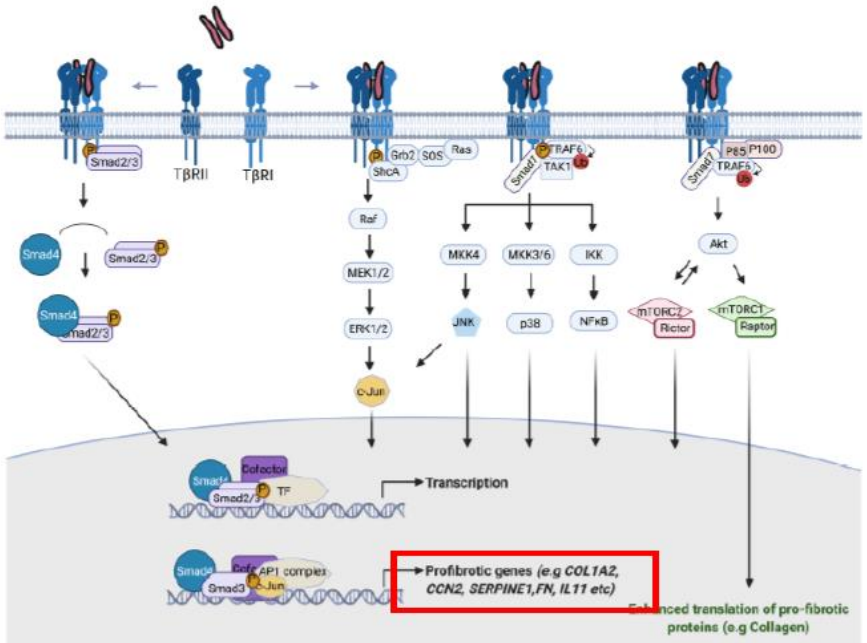
  - Transgenic mice develop colitis and intestinal fibrosis
  - Murine anti-TL1A antibody alleviates inflammation and fibrosis
  - Variants in the TL1A-encoding gene (TNFSF15) are associated with increased IBD risk
    - TL1A likely a differential disease driver in a subgroup of IBD patients
    - Genetically-based diagnostic test being developed to identify patients with higher likelihood of response



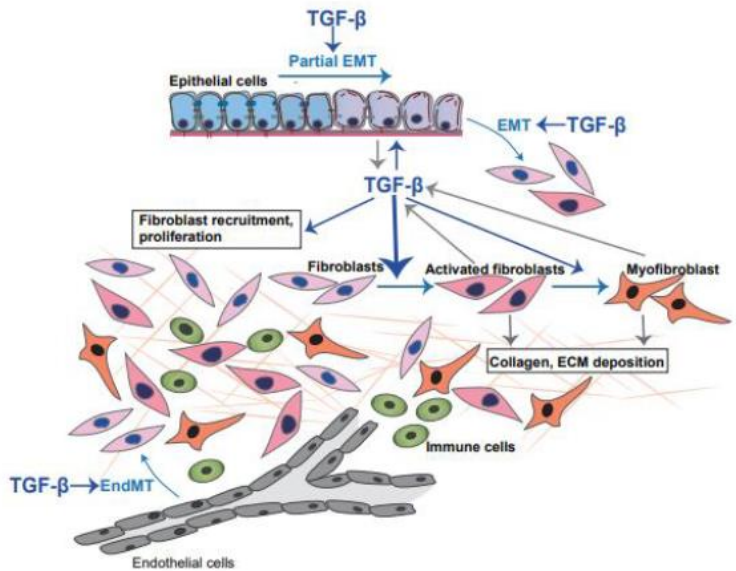
[1]Ruuls et al. Immunity 2001
[2] Yue et al. J Biol Chem 1999.
[3]Furfaro et al. Curr Drug Targets 2021.
[4]Xu et al. Front Immunol 2022.

MoA: TGF-β directly activates fibrogenic genes and EMT/endMT

- TGFβ directly activates transcription of fibrogenic genes such as **serpine-1 (PAI-1), IL-11, collagens** and **fibronectin**

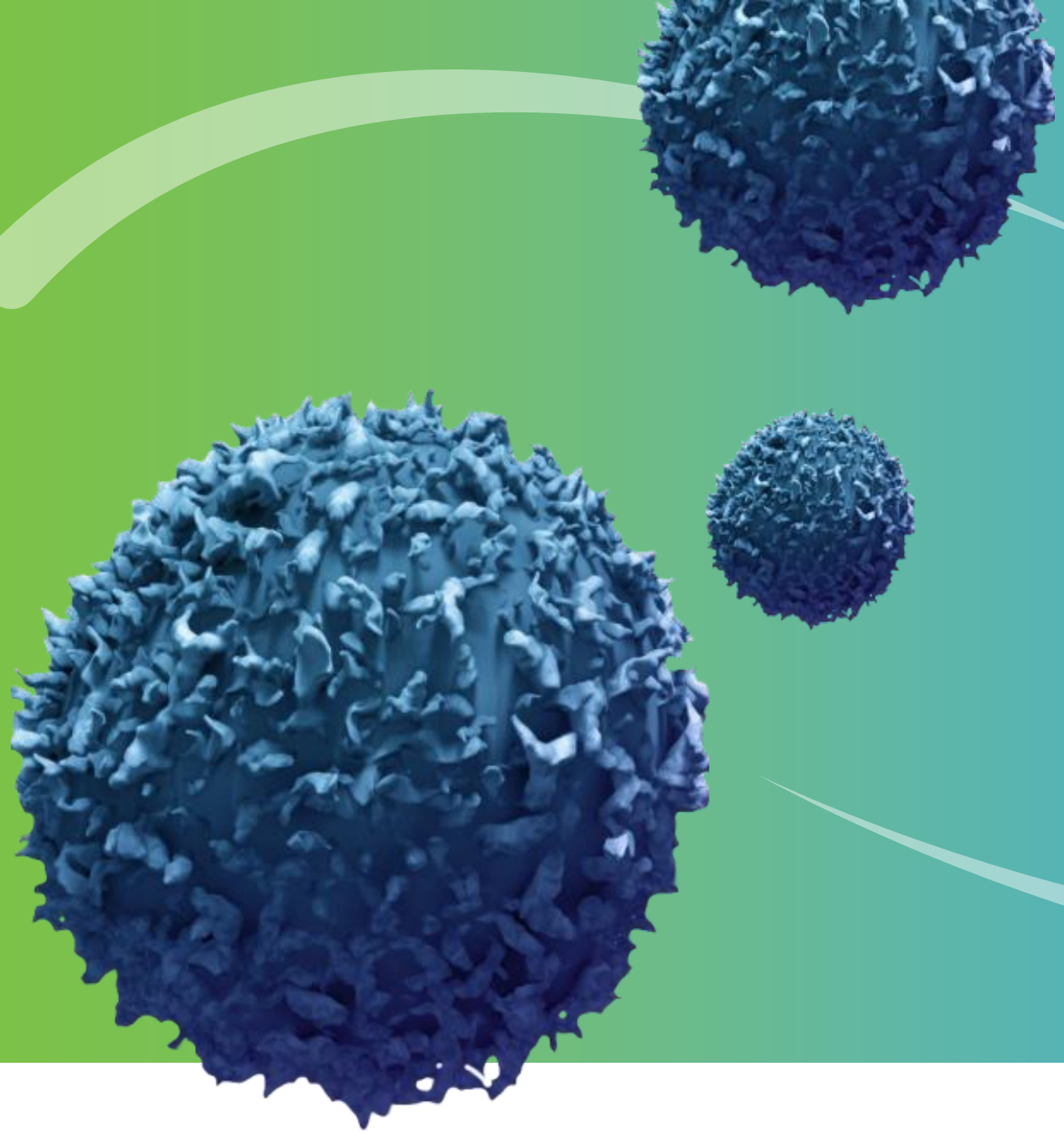


- TGFβ recruits but also generates new myofibroblasts from epithelial and endothelial cells through induction of EMT/EndMT
- TGF-β directly activates genes involved in EMT such as Snail



Conclusions

- Multiple new agents/approaches are on the horizon
- TL1A monoclonals, oral alpha 4 beta,7-IL-23s and mRNA silencing are exciting new therapeutic approaches
- Combination therapy is the new black! (two competing visions)
- Unique opportunities for new MOAs to provide novel combination
- Future is bright!



EQ504: Targeting AhR to Promote Mucosal Healing In Ulcerative Colitis

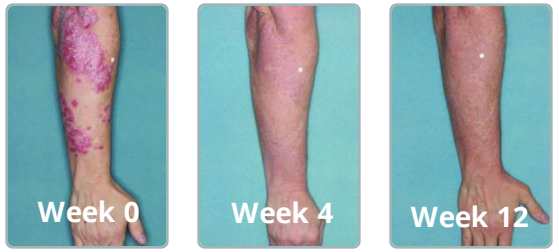
October 2025

Modulation of AhR Clinically Validated in Skin and GI Disease

VTAMA® (tapinarof) cream 1%

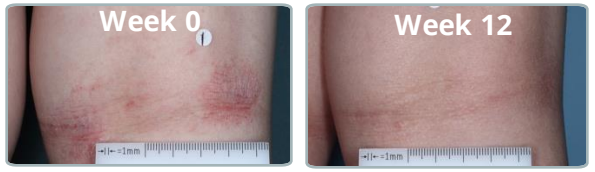
FDA Approved in Psoriasis

Up to 34% patients achieved a PGA-Pso score of 0-1 by week 12



FDA Approved in Atopic Dermatitis

Up to 34% patients achieved a vIGA-AD score of 0-1 by week 8



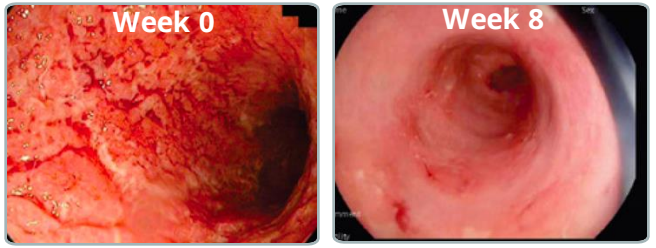
Indigo Naturalis

(botanical medicine containing indirubin)

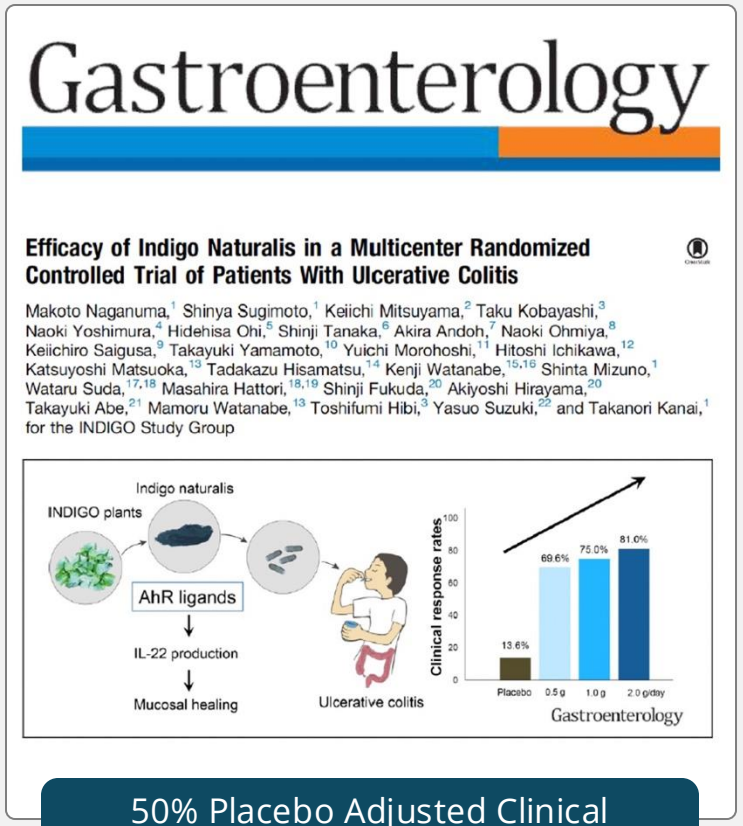
Phase 2 Trials in Ulcerative Colitis

Up to 50% patients achieved clinical remission with total Mayo score ≤ 2, no individual subscore > 1

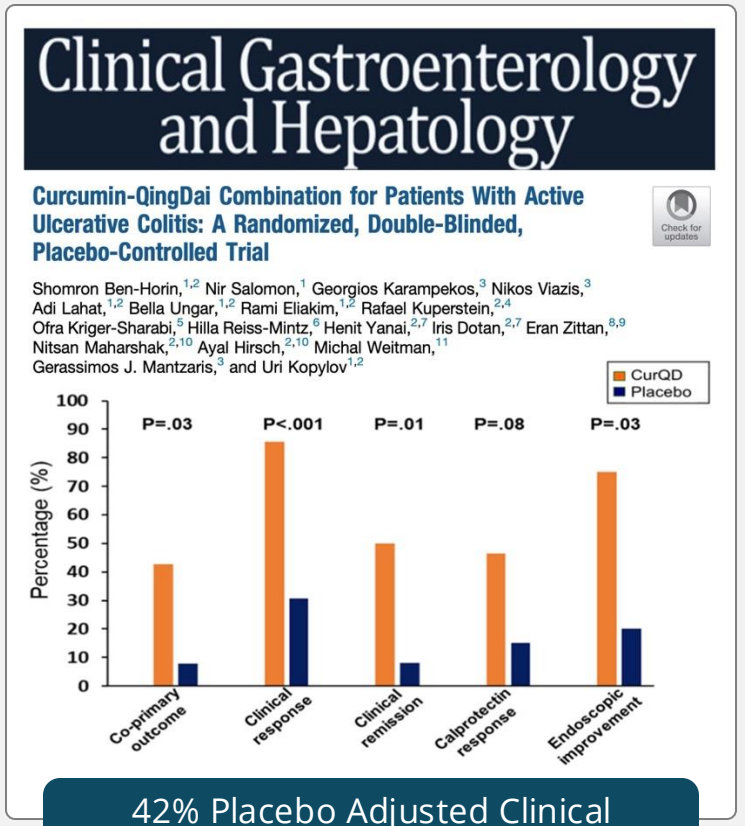
Up to 27% patients with treatment refractory disease achieved clinical remission with total Mayo score < 3, no individual subscore > 1



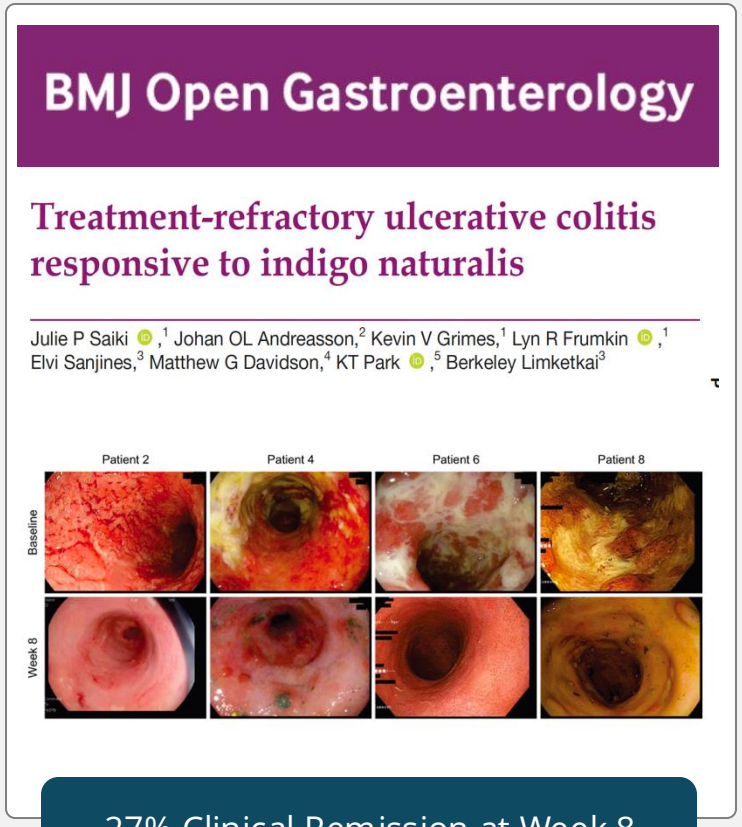
AhR Agonism Leads to High Rates of UC Clinical Remission



50% Placebo Adjusted Clinical Remission at Week 8



42% Placebo Adjusted Clinical Remission at Week 8



27% Clinical Remission at Week 8

Studies of ulcerative colitis patients treated with indigo naturalis demonstrate on-target engagement of AhR through increased intestinal CYP1A1 and high levels of clinical remission

EQ504 is a Potent Analog of ITE with Drug-like Properties

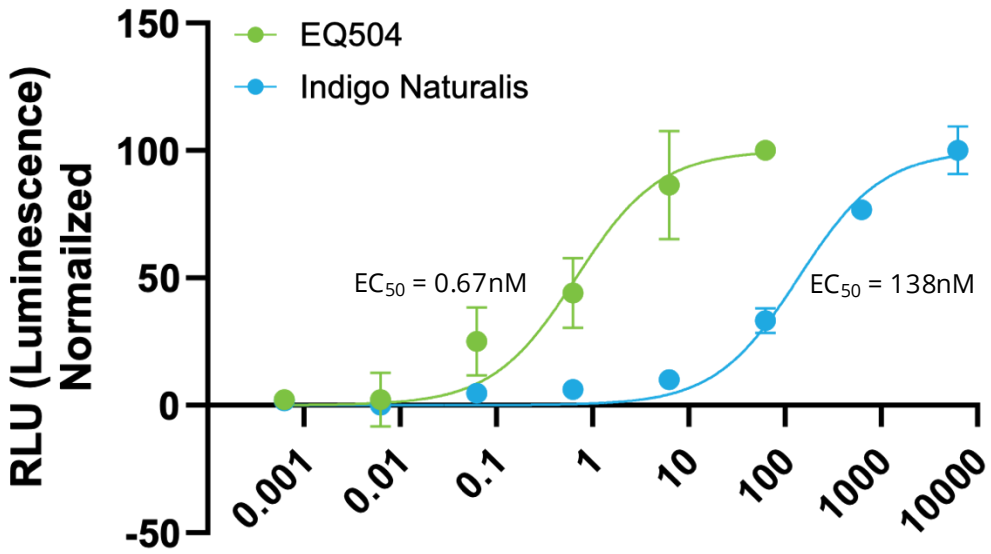
ITE is a naturally-occurring, endogenous, non-toxic AhR modulator synthesized in the gut & lungs

- Induces T_{reg} cells and IL-10, while reducing $T_{helper}17$ cells and inflammatory cytokines
- Induces IL-22 expression leading to improved barrier function and repair

EQ504, derived from ITE, is a highly potent and selective modulator of AhR

- Water soluble, GI stable with well-defined ADME, PK and PD properties
- Key IND enabling studies complete

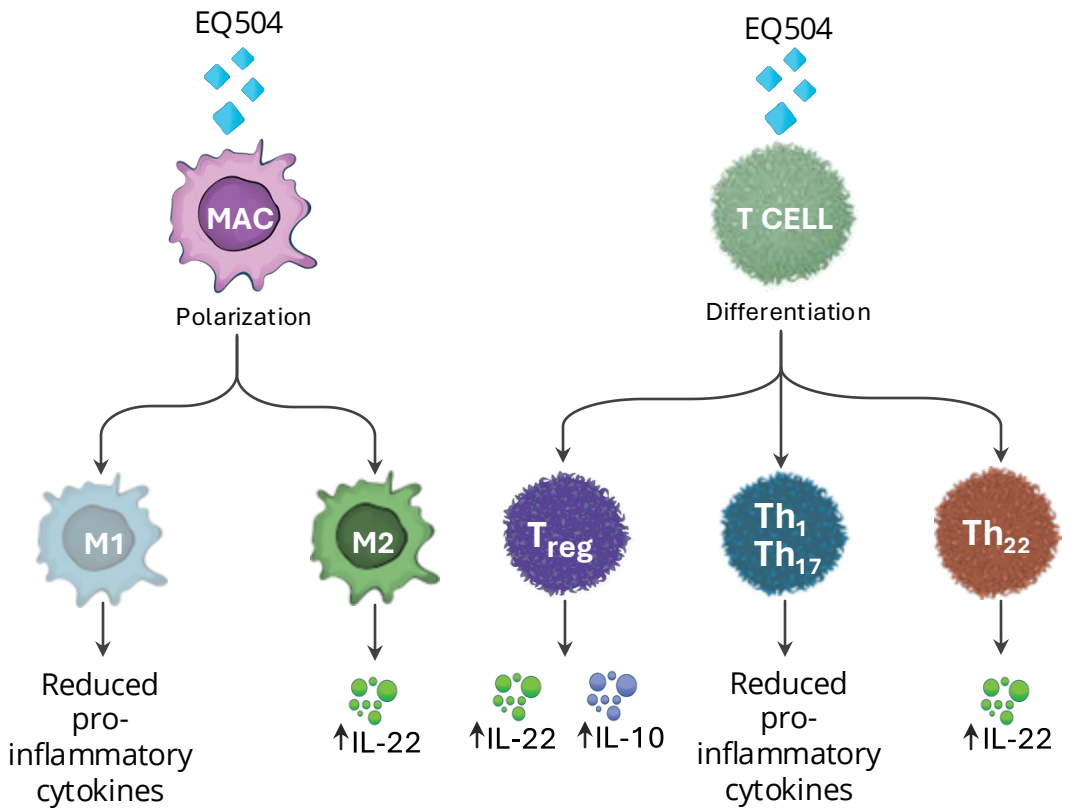
Induction of CYP1A1 in HepG2 (AhR-Lucia) Reporter Cells



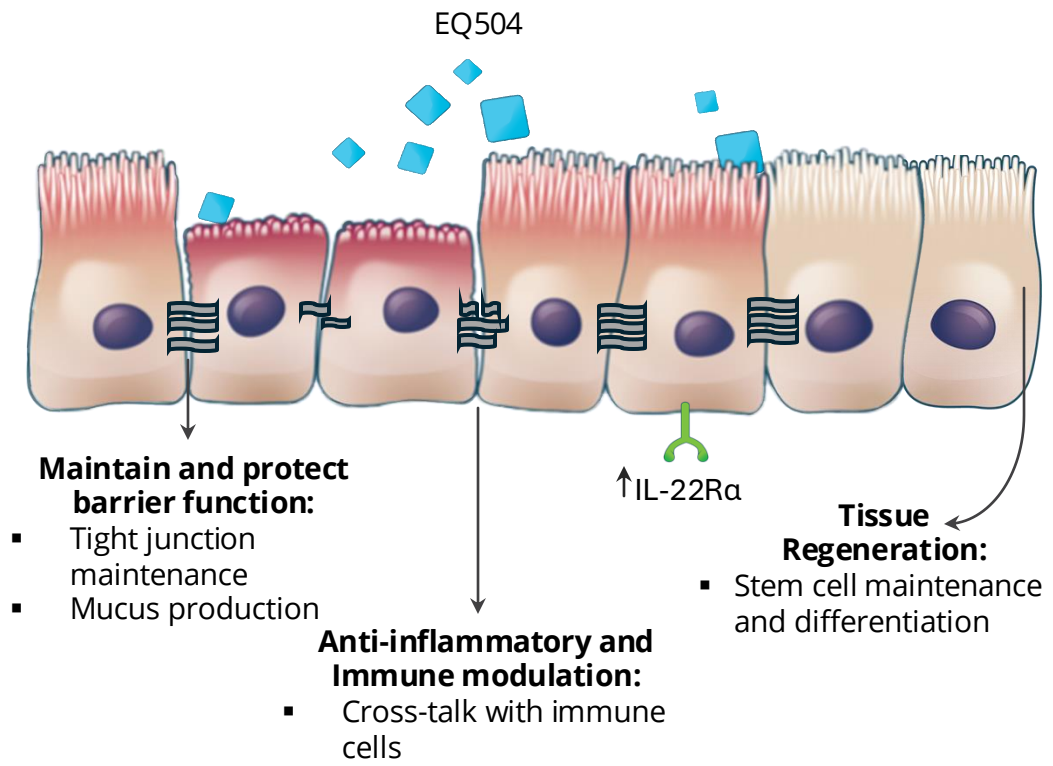
Abbreviations: GI, gastrointestinal; ADME, absorption, distribution, metabolism, and excretion; PK, pharmacokinetic; PD, pharmacodynamic; GMP, good manufacturing practices; 16:1 molar ratio of indigo to indirubin in indigo naturalis based on Saiki et al., BMJ Open Gastroenterol, 2021

Multi-modal Mechanism of Action in Mucosal Homeostasis

Modulates Immune Cell Responses



Barrier function & Tissue Repair



Maintain and protect barrier function:

- Tight junction maintenance
- Mucus production

Anti-inflammatory and Immune modulation:

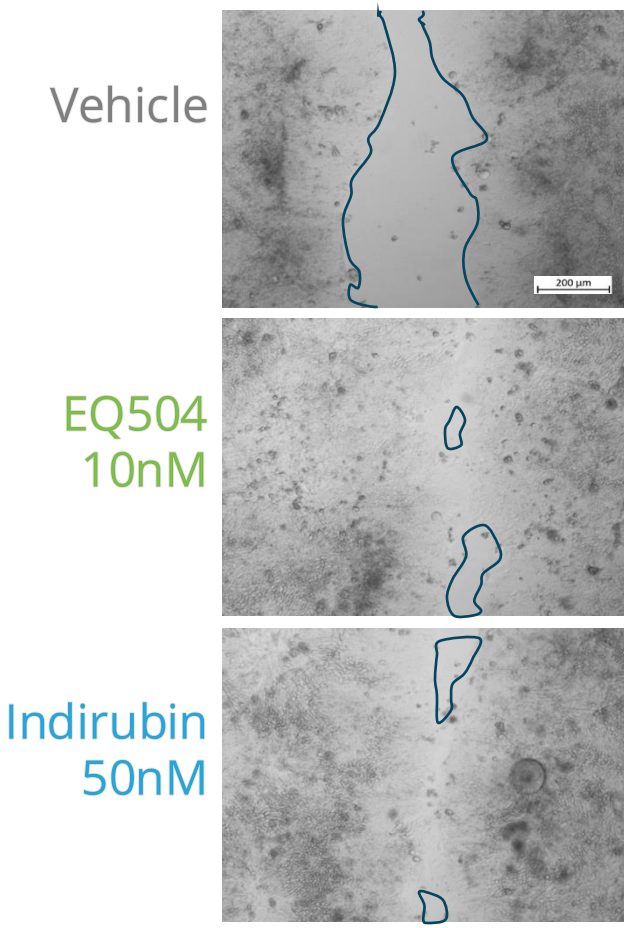
- Cross-talk with immune cells

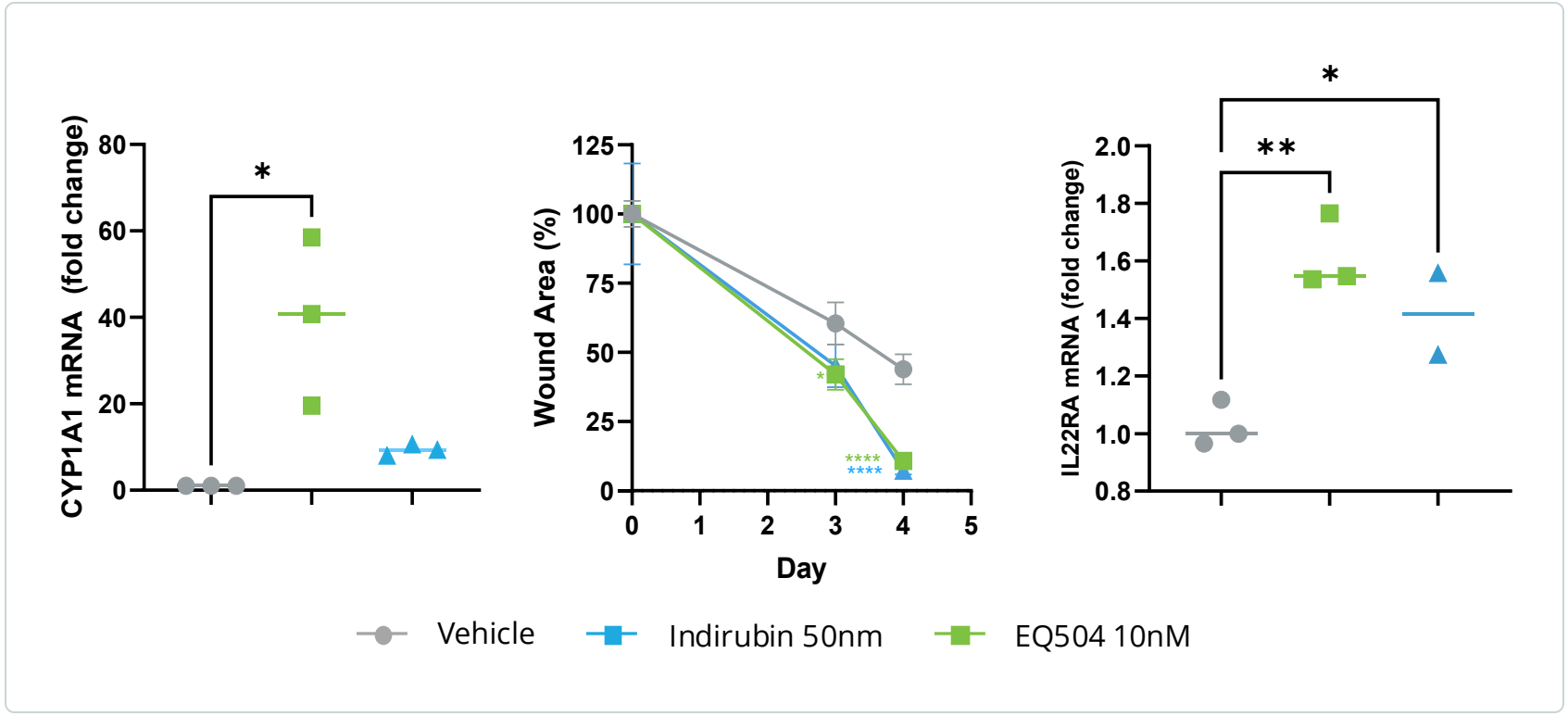
Tissue Regeneration:

- Stem cell maintenance and differentiation

EQ504 Promotes *Ex Vivo* Intestinal Epithelial Wound Healing

T84 Call Scratch Assay

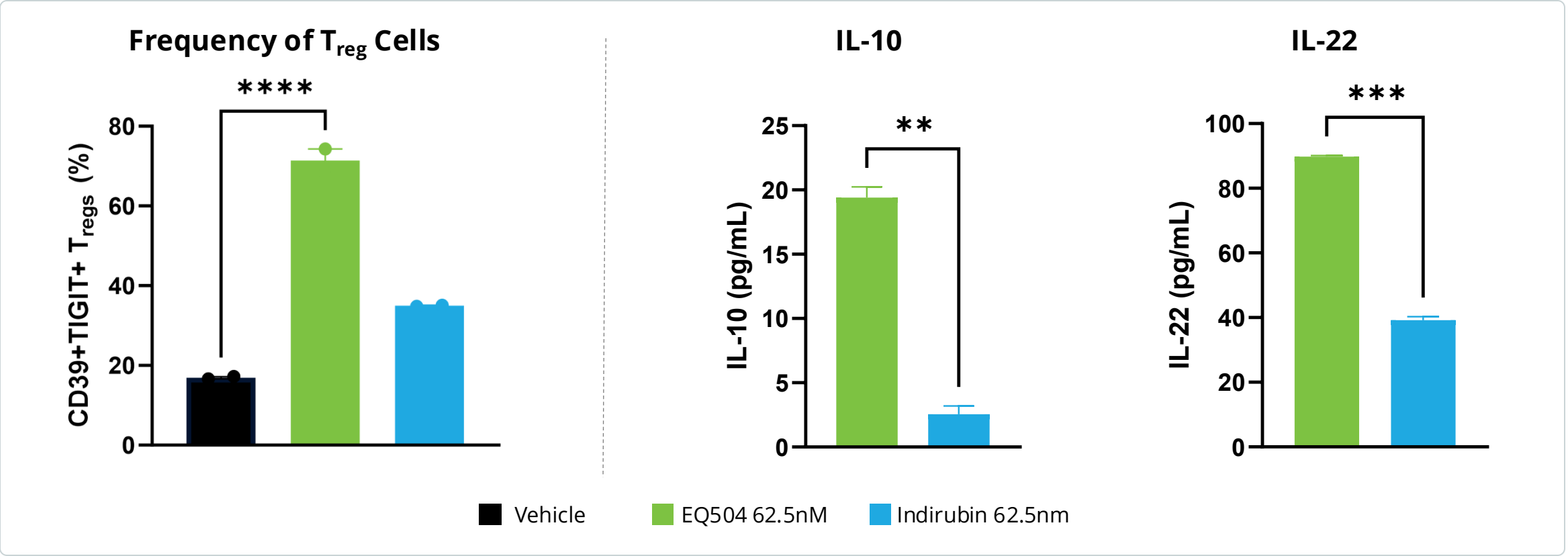




Modulation of AhR (CYP1A1) induces IL-22, which leads to increased levels of wound healing

****p<0.00001, **p<0.001, *p<0.005 vs Vehicle by Two-way ANOVA. T84 cells in a standard scratch assay, see Lanis et al., Mucosal Immunol, 2017.
In-house data, Marrocco et al., American Association of Immunologists, 2025

EQ504 Modulates T_{reg} Cells and Cytokine Expression *In Vitro*



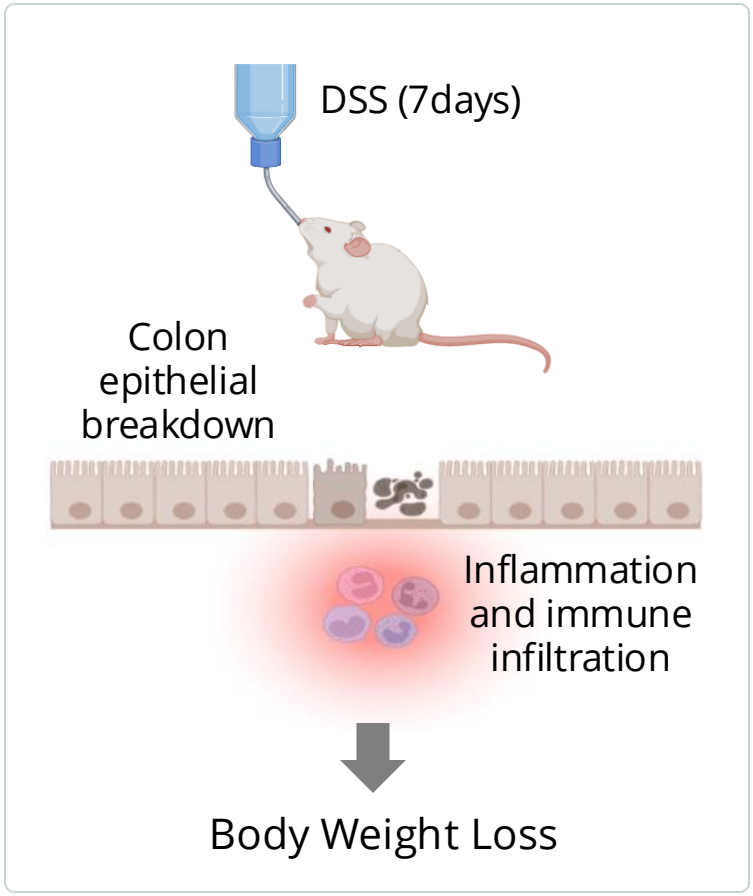
EQ504 increases the number and function of suppressive T_{reg} cells that inhibit activity of T_h1 and T_h17 cells and promote tissue homeostasis

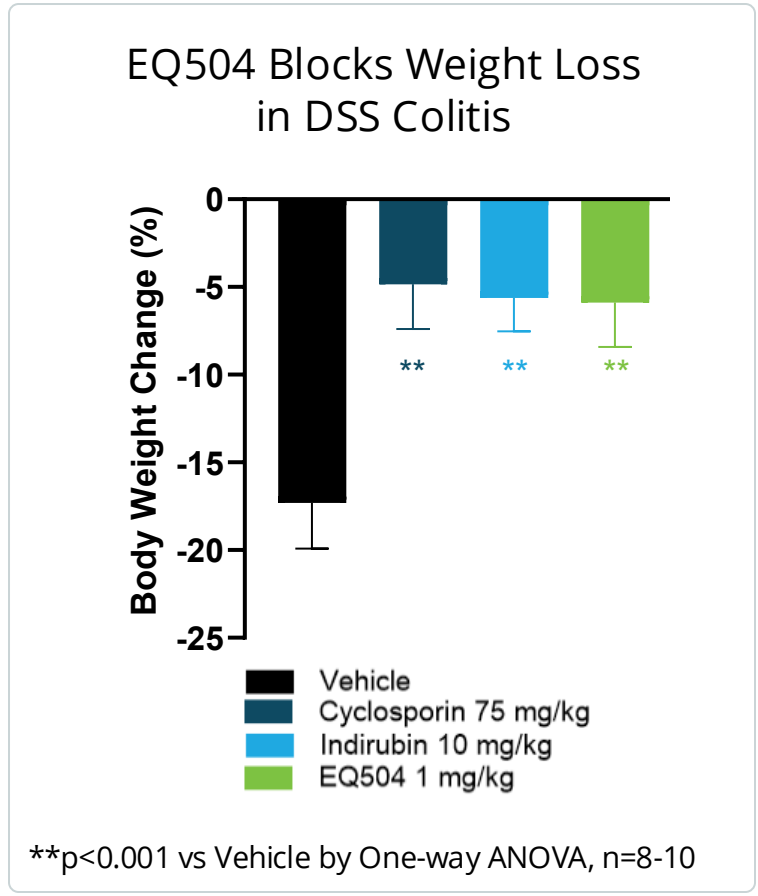
*****p<0.0001 ,***p<0.001; one-way ANOVA*
T_{reg} define as CD4+CD25hiCD127lo. Naïve T cells are differentiated under standard T_{reg} differentiating conditions; retinoic acid + TGFB (cocktail) with a low CD3/CD28 stimulation for 7 days. TGIT+ T_{reg} cells selectively inhibit pro-inflammatory T_h1 and T_h17 cells (Joller et al., 2015), while $CD39^{hi}$ T_{reg} cells have stronger stability and function under inflammatory conditions (Gu et al., 2017).
Ampudia et al., American Association of Immunologists, 2025 (Poster 107)

EQ504 Demonstrates Activity in Treating Colitis *In Vivo*

DSS Colitis Animal Model

- DSS-induced colitis is the most widely used *in vivo* model of UC
- CSA is a broad and strong immuno-suppressant, used as a positive control
- Indirubin is efficacious at 10 mg/kg in the DSS model
- EQ504 is efficacious at 1mg/kg in the DSS model
- Human equivalent dosing of approximately 5mg total

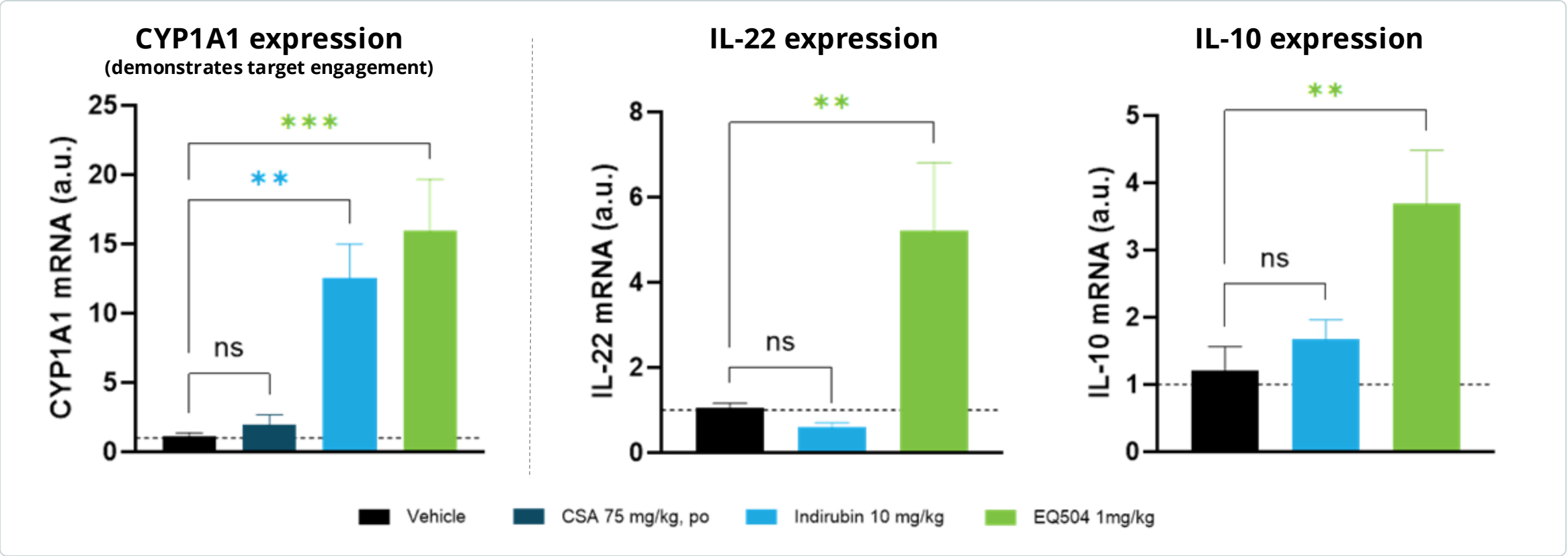




**p<0.001 vs Vehicle by One-way ANOVA, n=8-10

Eicheke et al., World J Gastroenterol 2017; Gao et al., Acta Histochemica 2016; DSS: Dextran Sodium Sulfate; IBD: Inflammatory Bowel Disease,; CSA: cyclosporin; In-house data, Chu et al., American Association of Immunologists, 2025

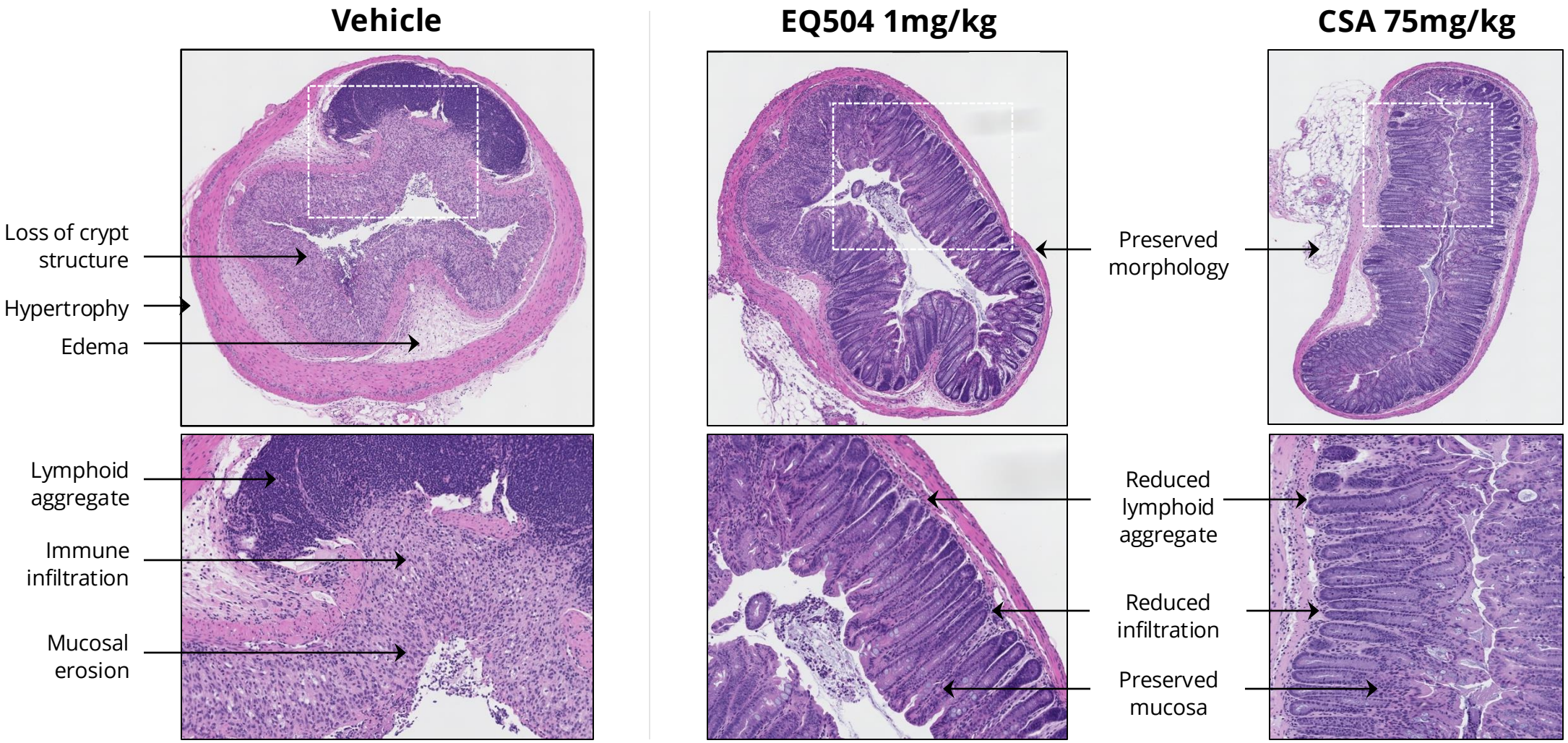
EQ504 Induces Anti-Inflammatory Cytokines in Colon Tissue



AhR modulators EQ504 and indirubin activate AhR pathways as demonstrated by increased CYP1A1 and anti-inflammatory cytokine expression in mouse colons with DSS colitis

***p<0.0001, **p<0.001 vs Vehicle by One-way ANOVA, n=8-10; In-house data, Chu et al., American Association of Immunologists, 2025

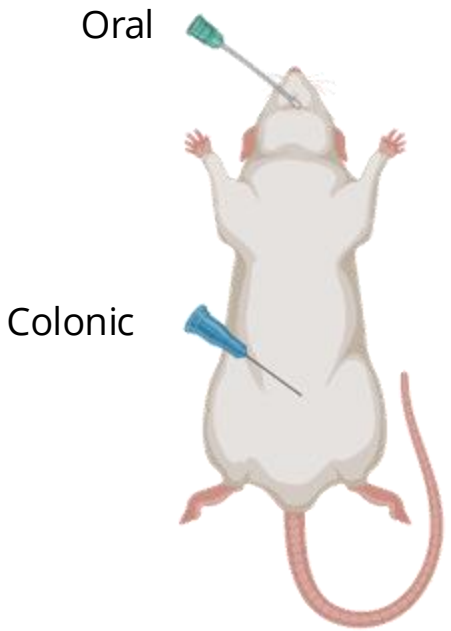
EQ504 Protects the Intestinal Mucosal Barrier in DSS Colitis



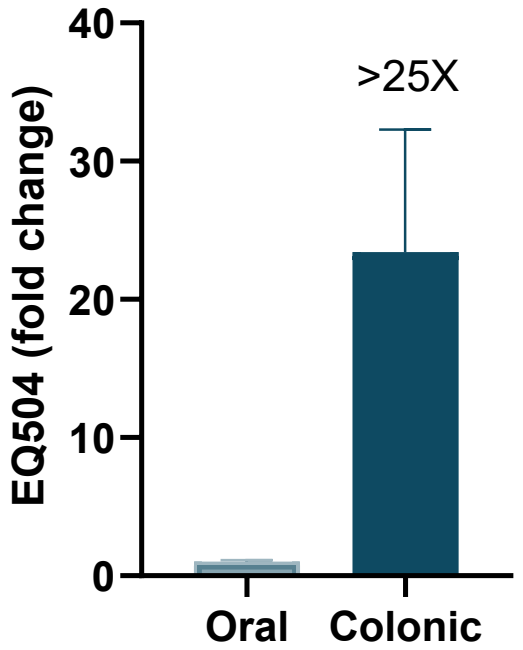
Sections taken from distal colon at day 10 in acute DSS mice

Colonic Delivery of EQ504 Reduces Systemic Exposure

Routes of Administration



Peak Colonic versus Systemic Exposure

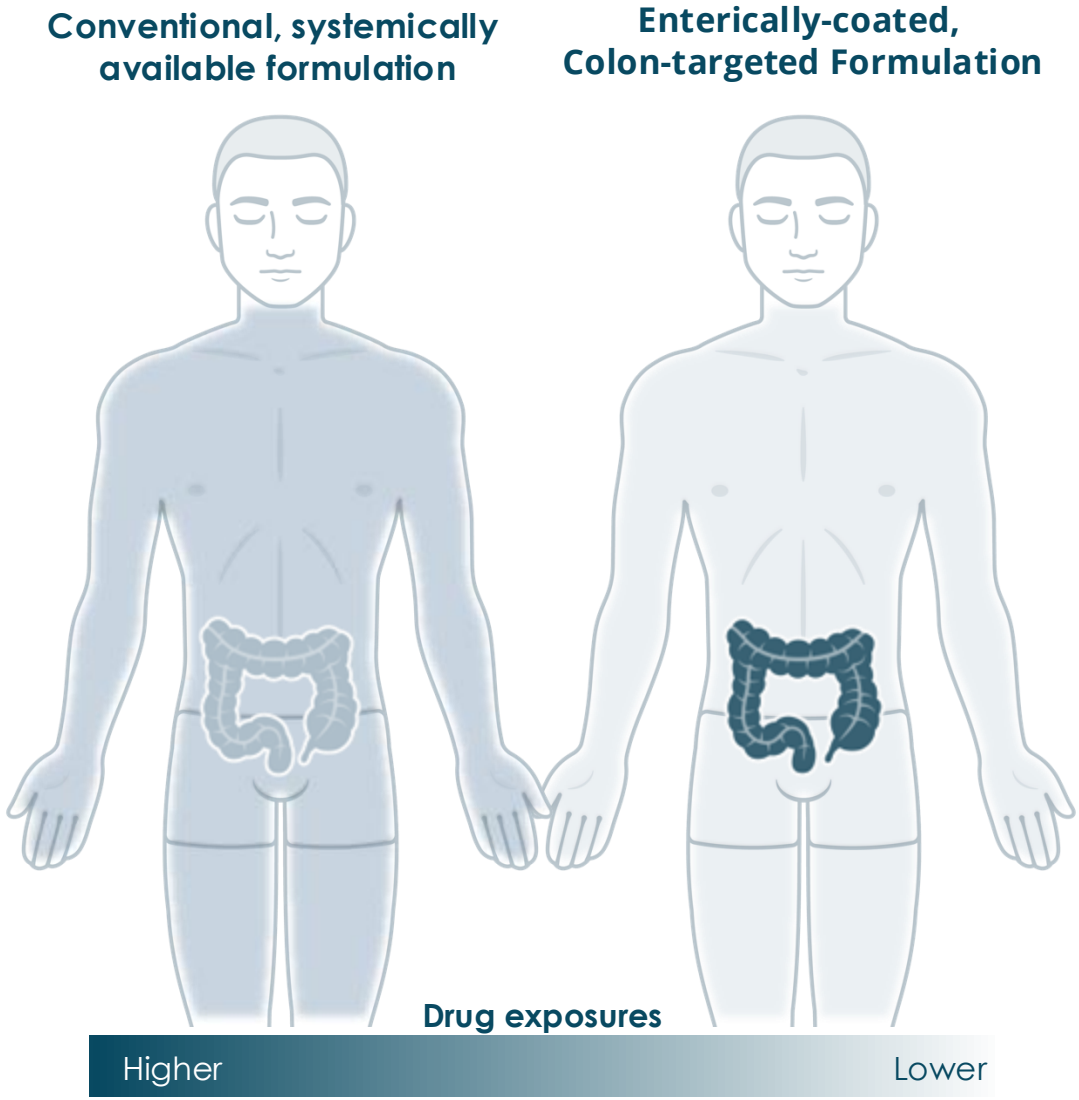


In vivo experiments demonstrate localized delivery of EQ504 directly to the colon of rats, results in 25x greater peak exposures in colon tissues versus blood

EQ504 in 2% HPMC and 0.1% Tween-80 and delivered by either oral gavage or via colonic cannula in Male SD rats (n=3 /group). Concentration was measured by LC/MS from colon tissue and blood plasma at 3, 6, 24hrs post dose. Peak exposures were analyzed as a ratio of colonic/systemic concentration and expressed as fold increase in colonic route vs oral route.

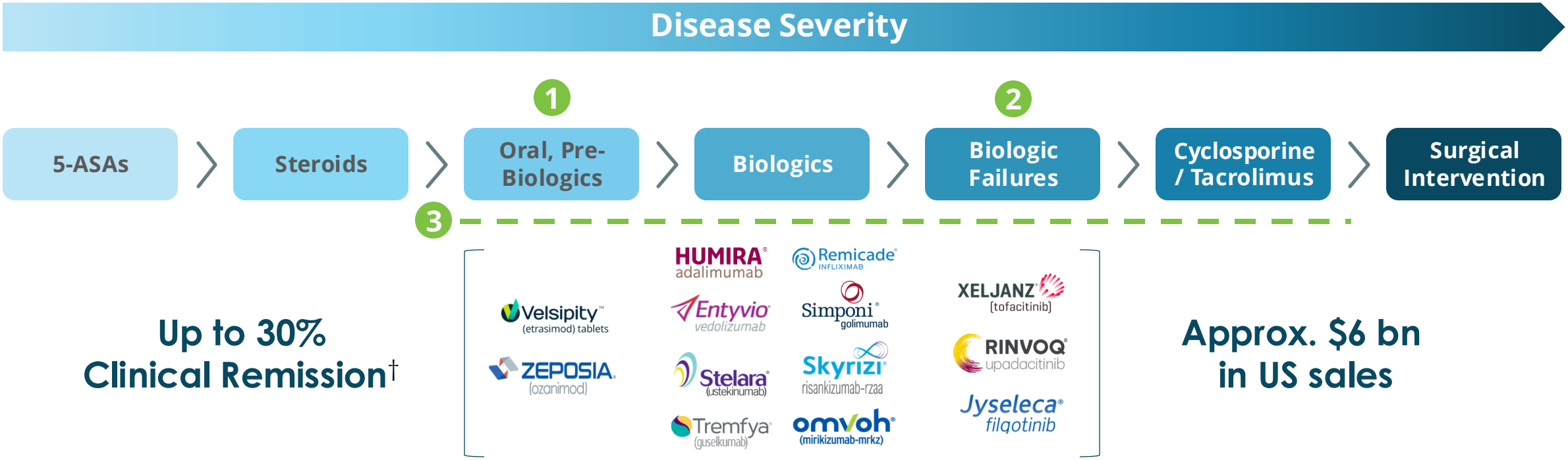
Targeting the Colon to Treat Ulcerative Colitis

- Targeting the colon in UC patients is a clinically and commercially validated approach e.g., 5-ASA's and steroids
- Colon targeting is achieved using enteric coating systems that dissolve at the start of the colon
- Targeted, localized treatment of the colon has several potential therapeutic benefits in UC:
  - Allows for optimization of dosing to target tissues: higher tissue and lower systemic exposures
  - Potential to expand therapeutic window with improved safety and tolerability profile



High Unmet Medical Need & Large Market Opportunity

EQ504 positioned to have significant utility across multiple lines of therapy



1 **Pre-biologic:** Substantial unmet need for new oral agents in the pre-biologic setting

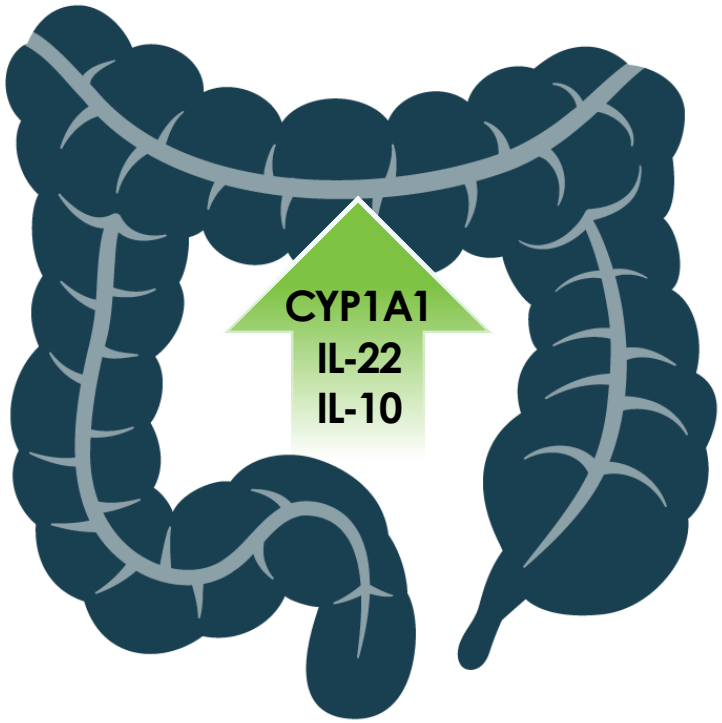
2 **Biologic failures:** Robust efficacy may support incremental opportunity in biologic failure patients

3 **Combination therapy:** MoA affords rationale for combination with current lines of immuno-modulatory therapies

Abbreviations: ASA, aminosalicylic acid; MoA, mechanism of action

Potential to Create Value in Early Clinical Development

- Multiple clinical studies of indigo naturalis establish strong proof of efficacy of AhR modulation (CYP1A1)
- Planning to conduct SAD/MAD proof of mechanism study
  - Safety, tolerability
  - Blood and tissue pharmacokinetics and pharmacodynamics
  - Target engagement & activity in colon biopsies by CYP1A1, IL-10, IL-22
- Phase 1 study initiation expected mid-2026
- Potential to achieve proof of concept with addition of UC patient cohorts following SAD/MAD



Nagmura et al., Gastroenterology, 2018; Saiki et al., BMJ Open Gastroenterol, 2021; Ben-Horin et al., Clin. Gastroenterol. Hepatol, 2024
Abbreviations: SAD/MAD, single ascending dose/multiple ascending dose; UC, ulcerative colitis; AhR, aryl hydrocarbon receptor

EQ504 Addresses Gaps in the UC Therapeutic Landscape

A differentiated approach to treating UC with clinical validation and clear biomarkers

Clinical Validation	AhR agonism in UC patients yields high rates of clinical remission with clear target engagement markers in the colon
Specific, Selective AhR Modulator	EQ504 multi-modal MoA modulates AhR signaling pathways to reduce inflammation and promote mucosal healing
GI-targeted, Locally Delivered	Oral medication for targeted treatment of inflammation in colon aimed at maximizing tissue exposure and minimizing systemic exposures
Broad Positioning	Application both pre- and post-biologics and potentially well suited for multiple combination approaches

Q&A Session