

APPLIED | MOLECULAR | TRANSPORT

**R&D Day**  
Virtual Meeting  
October 15, 2021

**BREAKTHROUGH MEDICINES.  
THE NEXT AGE OF BIOLOGICS.**

# Forward-Looking Statements

This presentation and any accompanying oral presentation contain forward-looking statements that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “estimate,” “intend,” “may,” “can be,” “plan,” “potential,” “target,” “will,” “mission” or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. Such statements include, but are not limited to, the potential of, and expectations regarding the potential of, potential benefits of, and expectations regarding AMT’s technology platform, AMT-101 and AMT-126, statements regarding the market potential of AMT’s product candidates, statements regarding AMT’s Phase 2 clinical trials for AMT-101 and AMT’s Phase 1 clinical trials for AMT-126, including the timing of such trials, enrollment of such trials, milestones and expectations relating to data readouts from such clinical trials, and AMT’s ability to leverage its technology to expand its pipeline including our ability to expand our technology platform by developing therapies to treat respiratory diseases. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: the timing of the initiation, progress and potential results of our preclinical studies, clinical trials and our research programs; our ability to use and expand our technology platform to build a pipeline of product candidates; uncertainty of developing biologic therapeutics; our ability to advance product candidates into, and successfully complete, clinical trials; the timing or likelihood of regulatory filings and approvals; our estimates of the number of patients who suffer from the diseases we are targeting and the number of patients that may enroll in our clinical trials; the commercializing of our product candidates, if approved; our ability and the potential to successfully manufacture and supply our product candidates for clinical trials and for commercial use, if approved; future strategic arrangements and/or collaborations and the potential benefits of such arrangements; our estimates regarding expenses, future revenue, capital requirements and needs for additional financing and our ability to obtain additional capital; the sufficiency of our existing cash and cash equivalents to fund our future operating expenses and capital expenditure requirements; our ability to retain the continued service of our key personnel and to identify, hire and retain additional qualified personnel; the implementation of our strategic plans for our business and product candidates; the scope of protection we are able to establish and maintain for intellectual property rights, including our technology platform, product candidates and research programs; our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately; the pricing, coverage and reimbursement of our product candidates, if approved; developments relating to our competitors and our industry, including competing product candidates and therapies; negative impacts of the COVID-19 pandemic on our operations; and other risks. These risks are not exhaustive. New risk factors emerge from time to time and it is not possible for our management to predict all risk factors. Actual results may differ materially from those in the forward-looking statements as a result of a number of factors, including those described in the company’s filings with the Securities and Exchange Commission. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

This presentation concerns product candidates that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). Those product candidates are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.



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## Welcome

Tahir Mahmood, PhD  
Chief Executive Officer and Co-Founder

# Distinguished KOLs and AMT Presenters on Today's Call



**Peter Lipsky, MD**

*Rheumatology Specialist  
Former Scientific Director and Chief of the Autoimmunity  
Branch, NIAMS, National Institutes of Health*



**Brian Feagan, MD, FRCPC**

*Professor of Medicine, Departments of Medicine, Division  
of Gastroenterology, Epidemiology and Biostatistics  
Western University, Canada*



**Tahir Mahmood, PhD**

*Chief Executive Officer  
and Co-Founder*



**Randy Mrsny, PhD**

*Chief Scientific Officer  
and Co-Founder*



**Bittoo Kanwar, MD**

*Chief Medical Officer*



**Liz Bhatt**

*Chief Business and Strategy Officer*

# Today's Agenda

## Topic

## Presenter

Introductions and Corporate Vision

Tahir Mahmood, PhD

Technology Platform and Next Generation Applications

Randy Mrsny, PhD

Clinical Programs

IL-10 and IL-22 Biology

Treatment Landscape in IBD

Oral AMT-101 Overview

Peter Lipsky, MD

Brian Feagan, MD, FRCPC

Bittoo Kanwar, MD


Oral AMT-101 Commercial Opportunity

Liz Bhatt

The Future / Conclusion

Tahir Mahmood, PhD

Q&A



**Our Mission is to Create  
Novel, targeted Oral biologic  
therapeutics with Enhanced  
efficacy and safety profiles  
in Patient-friendly formats**

**A CLINICAL STAGE COMPANY**

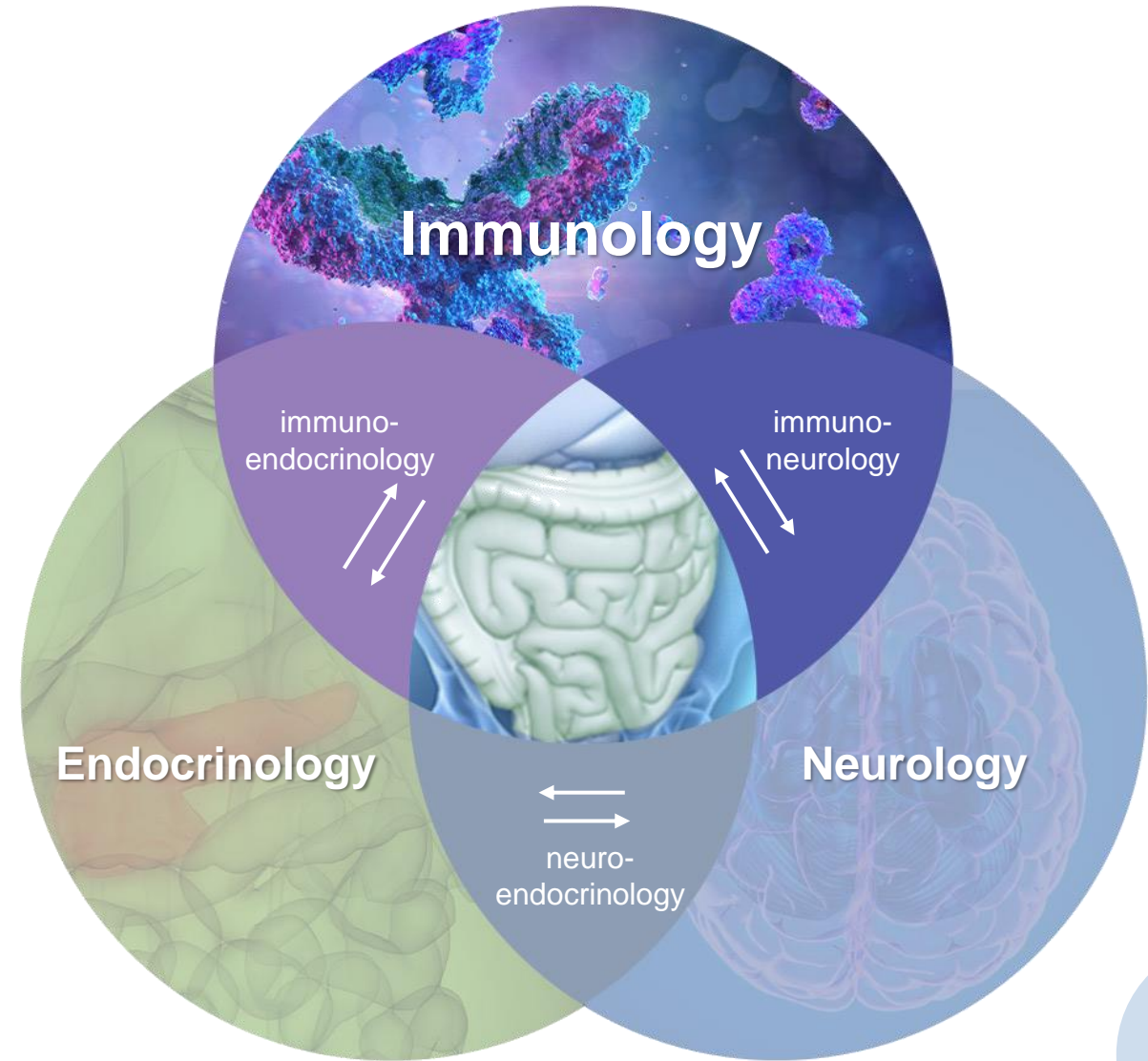
**WITH 2 PRODUCT  
CANDIDATES  
IN 5 CLINICAL TRIALS**



# ORAL ROUTE PROVIDES SIGNIFICANT BENEFITS

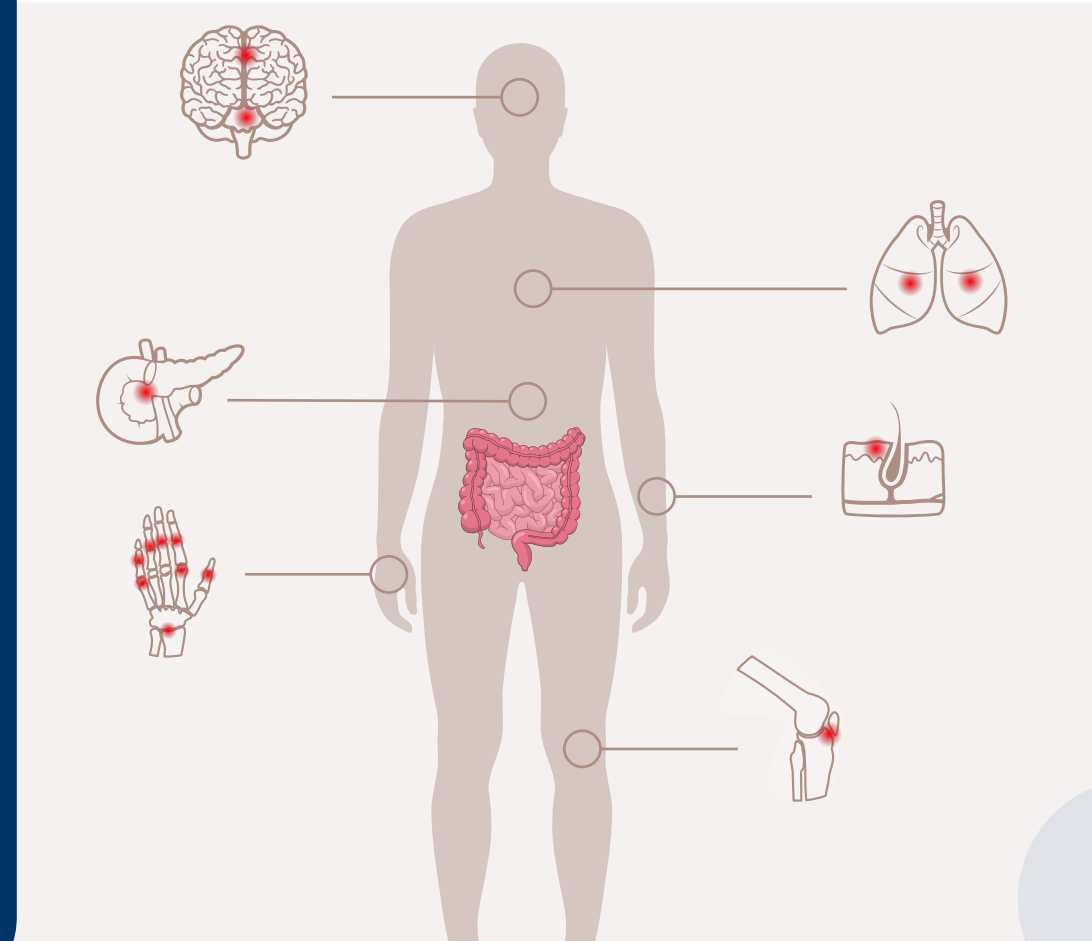
The gut is the primary site of convergence  
of core biology axes that impact virtually  
every organ system

~70% of the body's immune cells are  
housed in intestinal tissue



# Oral Targeting of GI Mucosal Immune System for Local *and* Distal Diseases

- Immune modulation and barrier defect repair
  - No immune suppression, minimal toxicity
- Multiple immune pathways to modulate in GI mucosa
  - Cell-trafficking, tolerance, autoimmunity
- Numerous immunological diseases:
  - **Local:** Ulcerative Colitis, Pouchitis, Crohn's Disease, Celiac Disease
  - **Distal:** Rheumatic Diseases, Multiple Sclerosis, Vaccines, Dermatology



Gracey, Nat. Reviews Rheumatology (2020): pp 415-433



# PLATFORM-BASED R&D

## An Efficient Engine for Generating Differentiated Oral Biologic Products



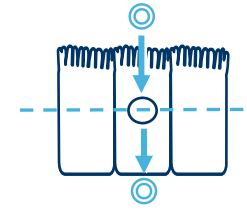
Leverage known targets  
to minimize risk



Maintain GI-selectivity to  
minimize any systemic  
safety concerns



Modulate systemic diseases  
via local GI effects



Exploit normal biology  
of transcytosis

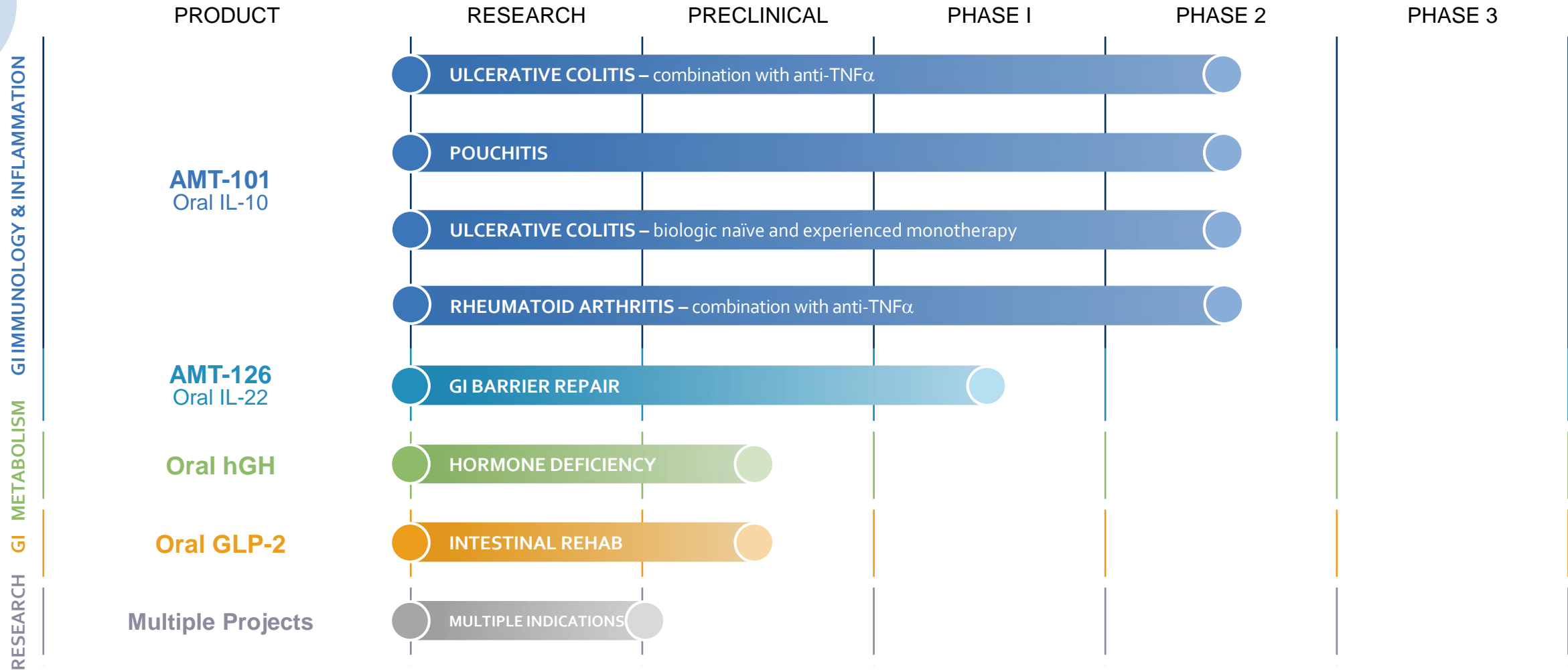


Interrogate local biology  
directly for enhanced effects



Select indications with  
unmet needs where  
oral administration is  
advantageous

# AMT Pipeline: Two Oral Biologic Therapeutics in the Clinic



AMT maintains worldwide rights to all product candidates and research programs.

# Significant Milestones Achieved Since IPO

2

Clinical Product  
Candidates

5

Active Clinical  
Trials

115+

Employees



Journal of Immunology  
Publication



ECCO Poster

IPO

\$177M

Follow-on

\$121M



AMT-101  
Phase 2 Start



AMT-126  
Phase 1 Start



Platform  
Expansion

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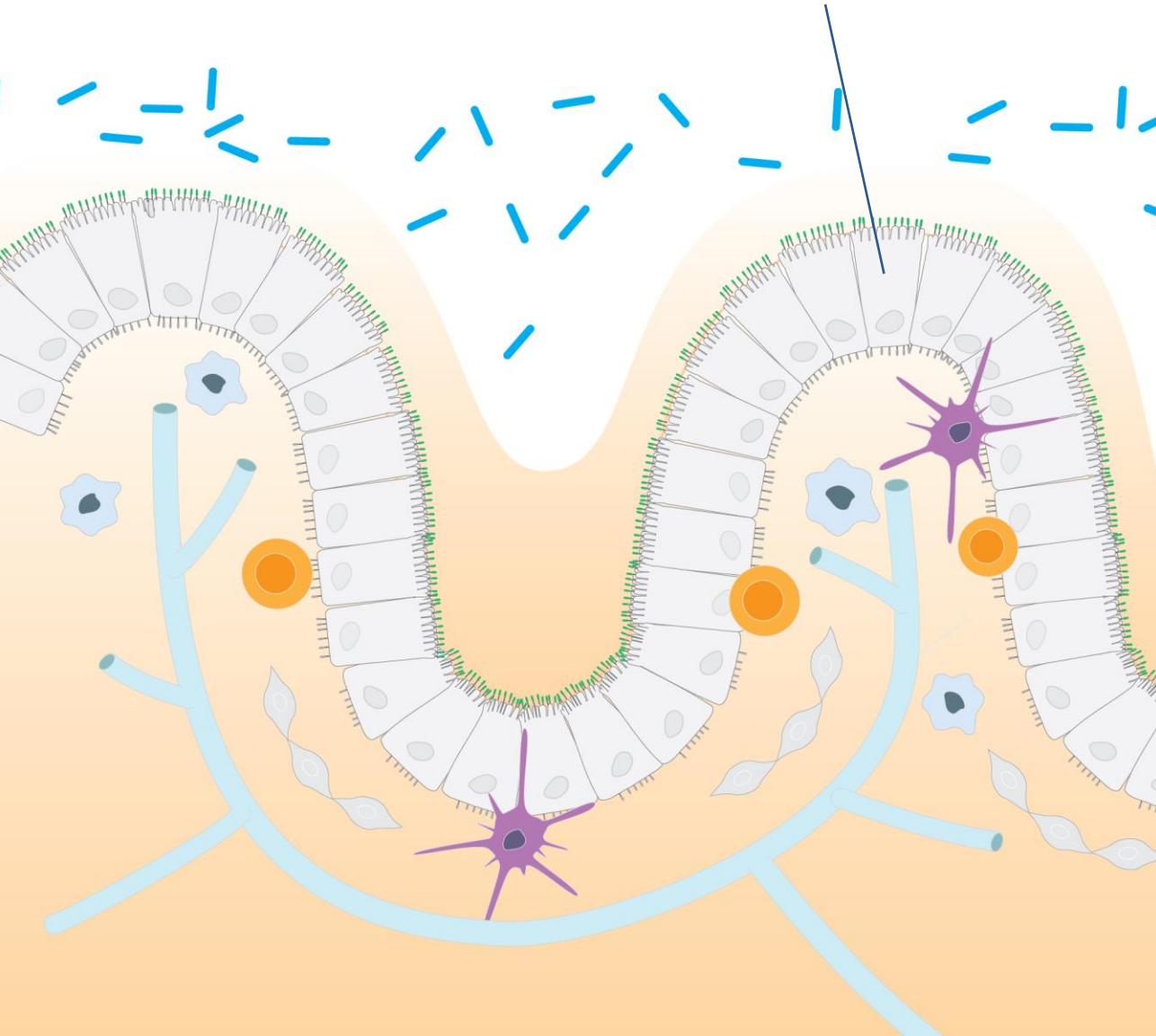


# AMT Technology Platform

Randy Mrsny, PhD  
Chief Scientific Officer and Co-Founder



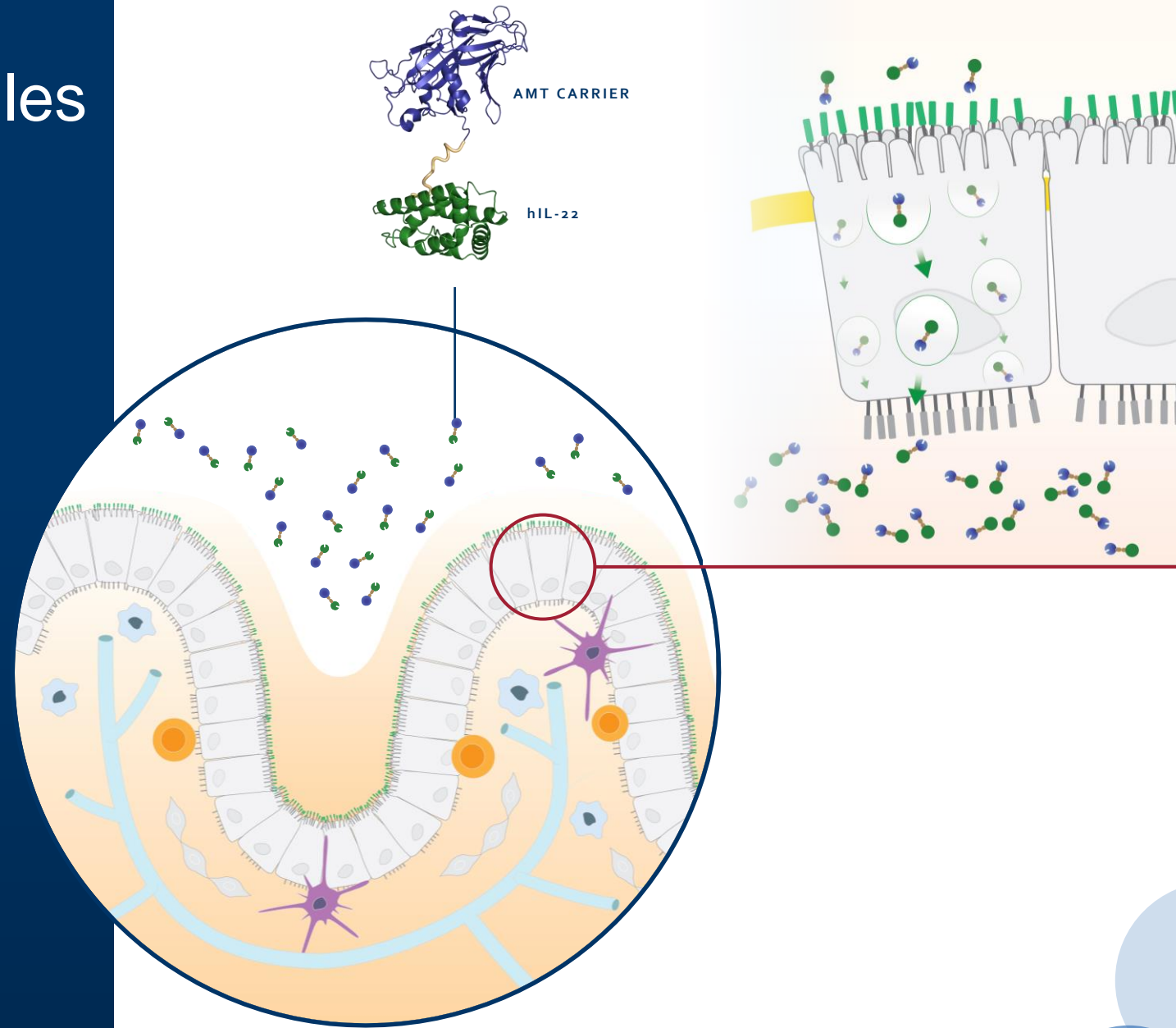
## INTESTINAL BARRIER



**THE CHALLENGE:**  
Intestinal epithelium  
is a natural barrier against  
protein, virus and bacterial entry

# Bioengineering Novel Molecules to Leverage Transcytosis - Nature's Transport System Through the Cell

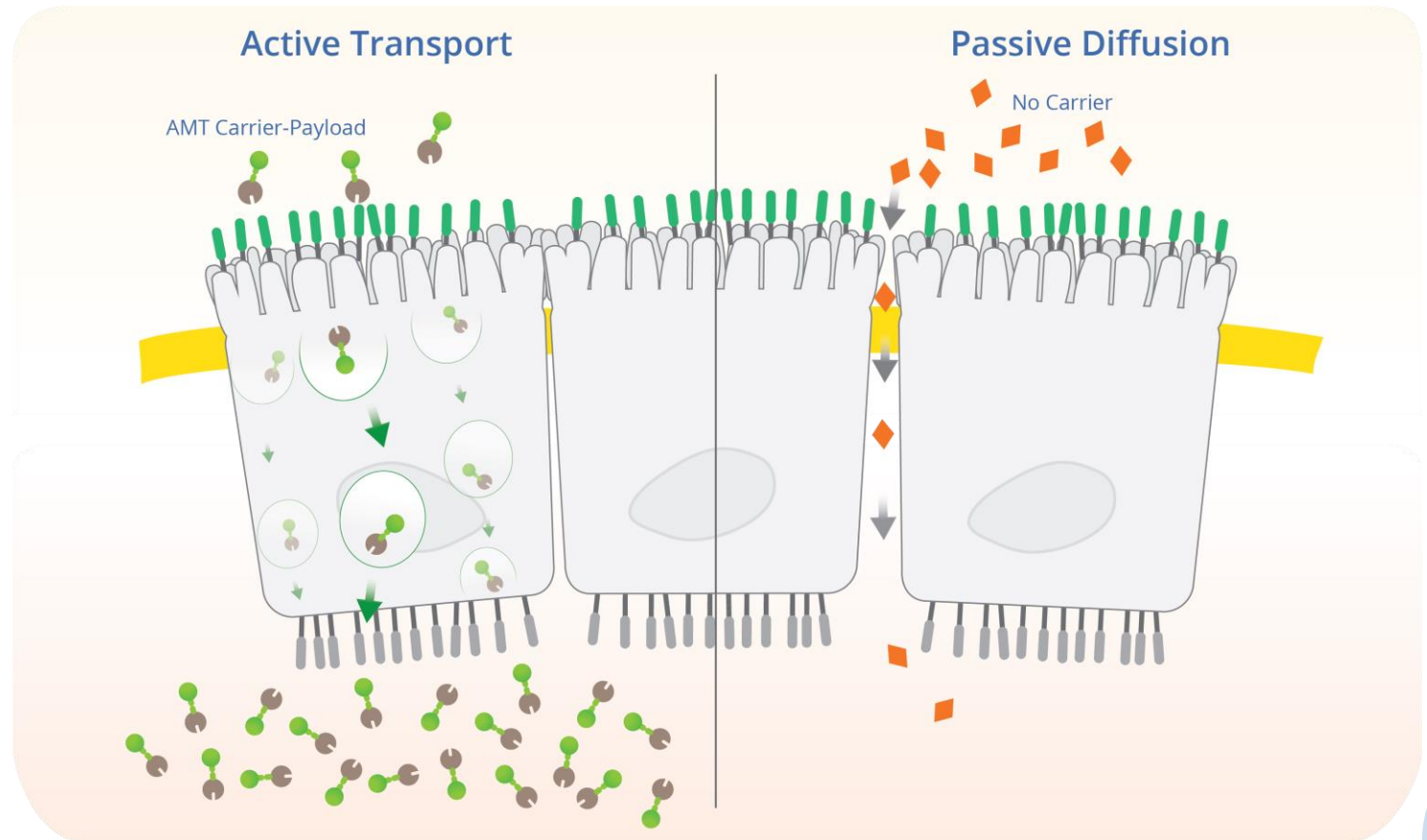
- Trafficking domain is derived from Cholix protein, that is secreted by *Vibrio cholerae*, and combined with a therapeutic payload
- Utilizes normal cellular machinery for moving select molecules through epithelial cells
- Active, rapid transport across GI epithelial barrier



# Advantages of Our Active Transport Mechanism

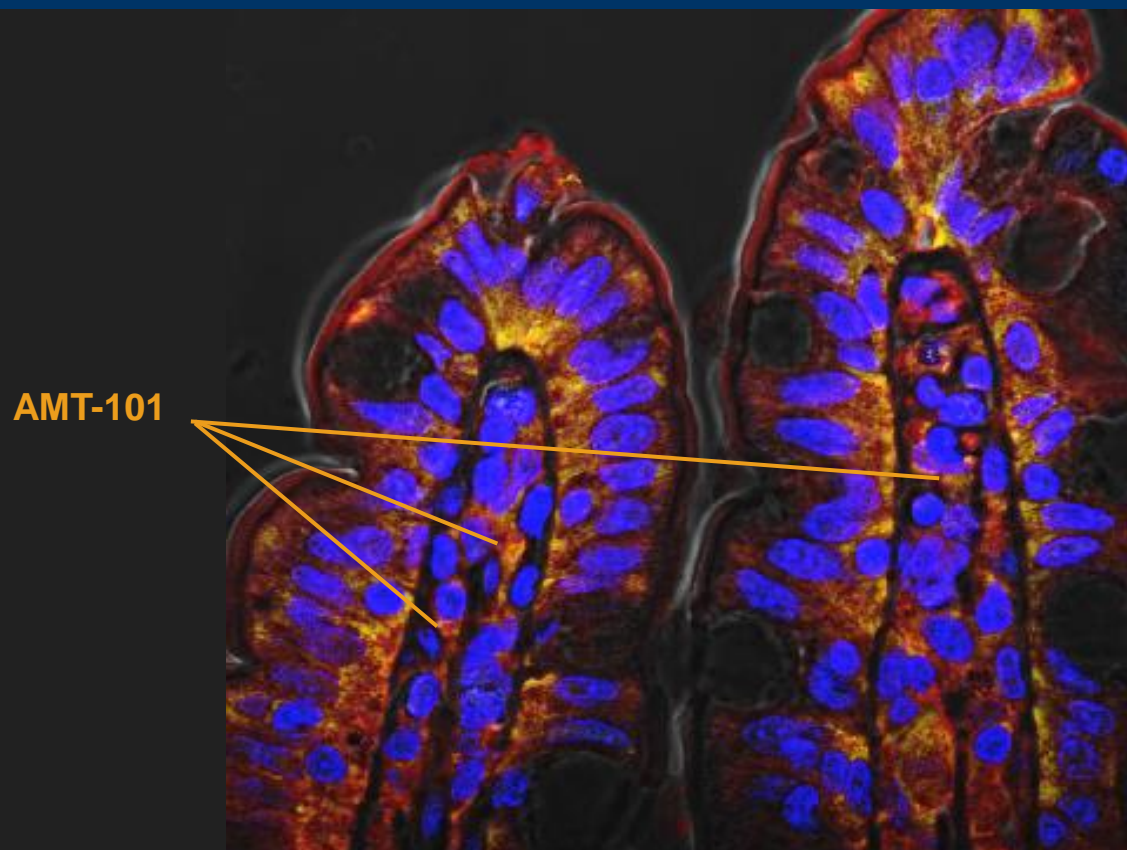
## Active Transport Vesicle-Mediated Trafficking

- High-capacity privileged pathway
- Rapid uptake across barrier
- Trafficking pathway accessible along entire length of GI tract
- Ability to localize in lamina propria tissue or release into circulation
- Compatible with multiple therapeutic modalities

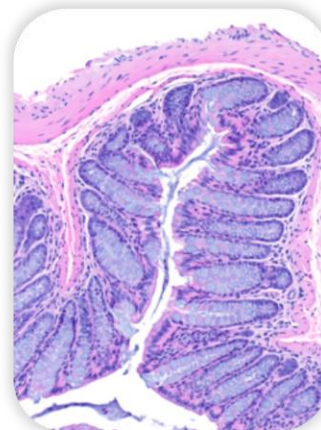




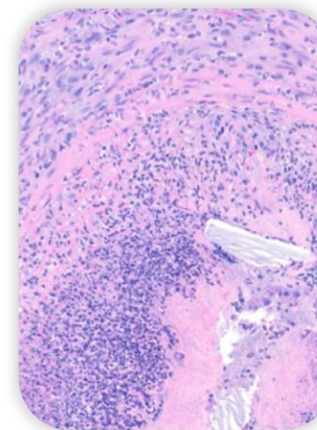
# AMT's Carrier Drives Active Transport Through the Intestinal Epithelium within Minutes



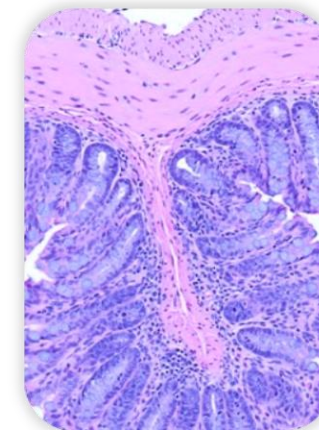
NAÏVE



VEHICLE



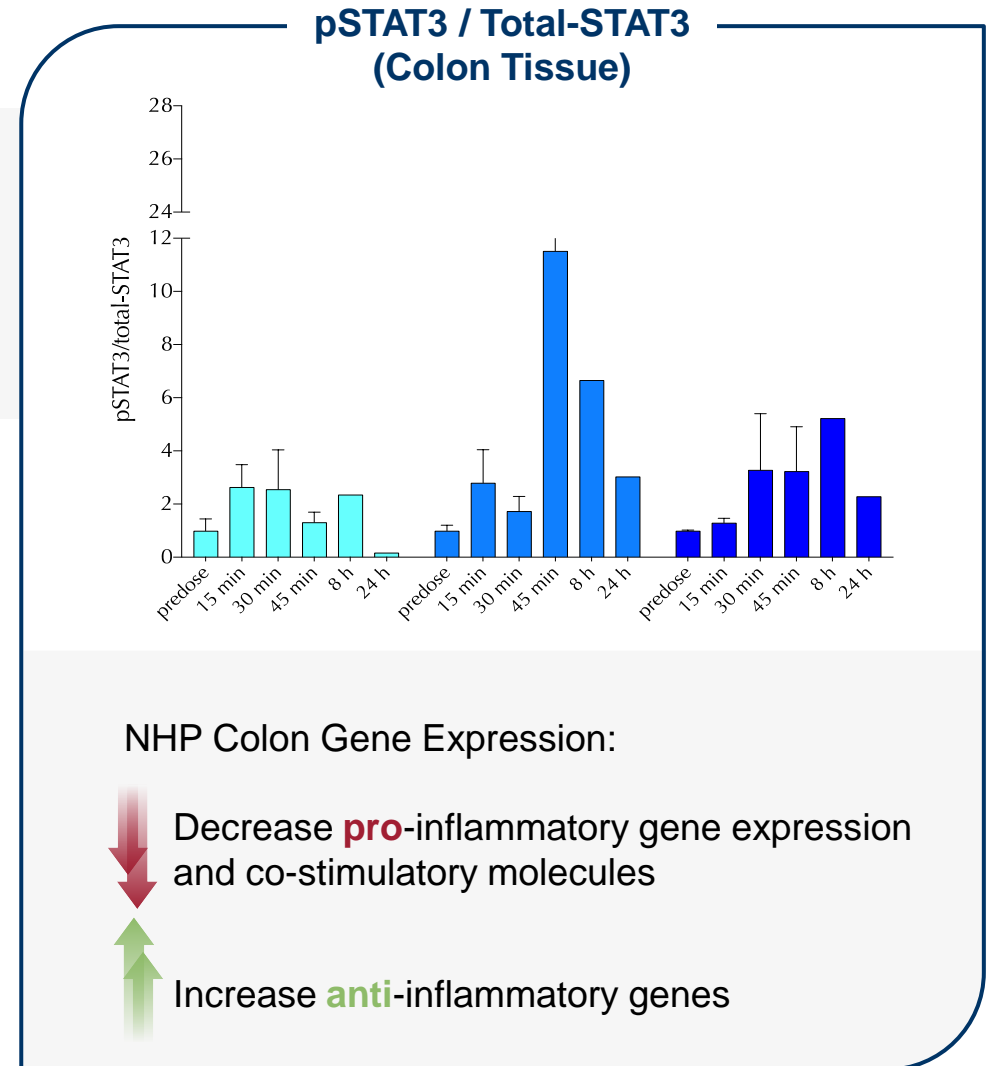
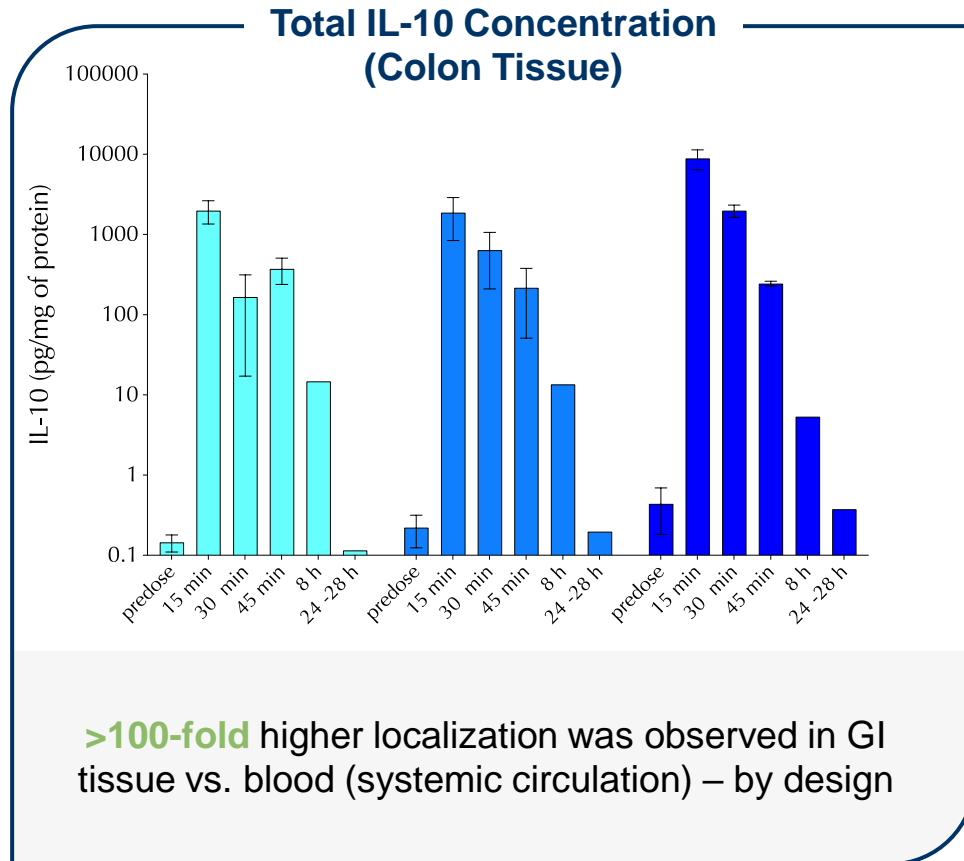
AMT-101



AMT-101 is trafficked in active form and acts locally in GI tissue, with efficacy observed in colonic tissue in murine models of colitis.

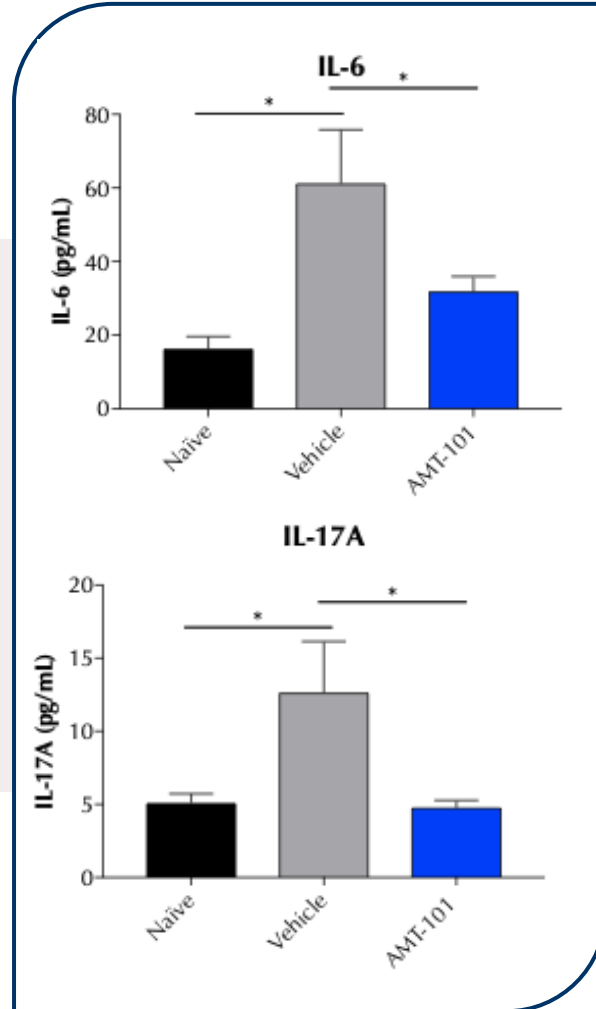


# AMT-101 (IL10-carrier fusion) In Vivo Localization and Activity in GI Tissue – Examples from Non-Human Primate (NHP)

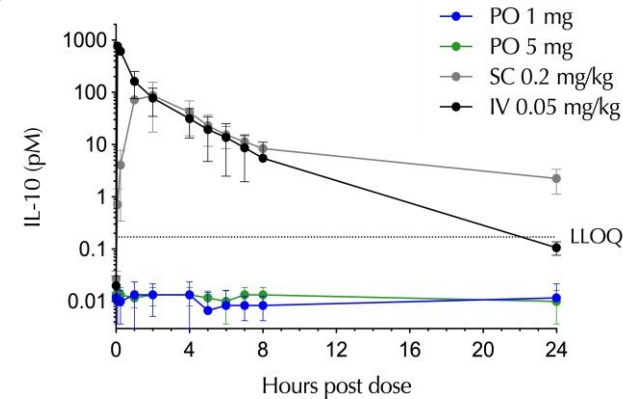


# Oral AMT-101 Regulates Systemic Markers of Inflammation and Immune Dysregulation Despite No Systemic PK

Serum levels of pro-inflammatory markers after treatment with AMT-101 in murine model of colitis

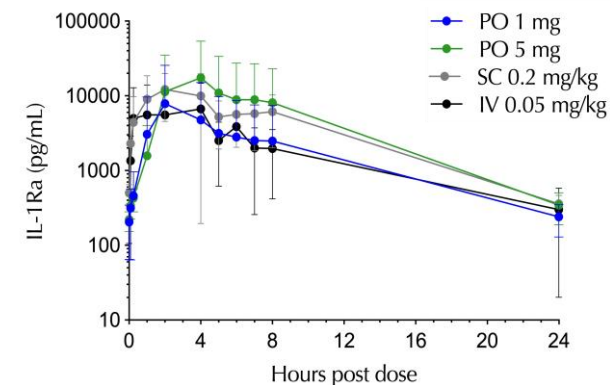


NHP: Minimal Systemic PK with Oral Administration



By design, AMT-101 remains in the lamina propria and acts locally

NHP: Robust Systemic PD with Oral Administration



In addition to acting locally, pharmacodynamic effects are observed in the blood compartment

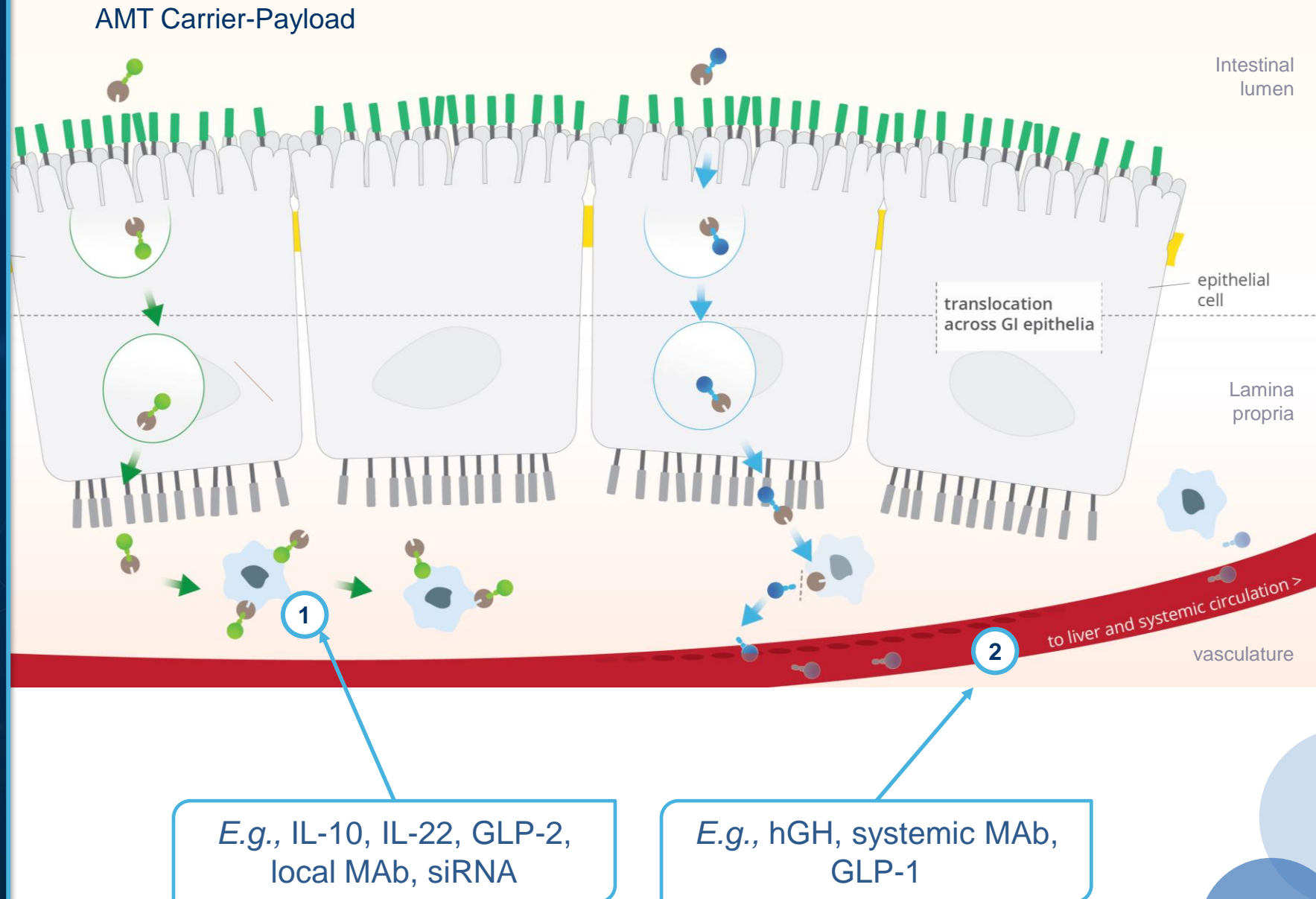
# AMT's Technology Platform can be Applied Across a Broad Spectrum of Therapeutic Modalities



Endogenous cellular trafficking vesicles diameter ~150 nanometers.  
As a result, the large vesicle size enables a broad range of therapeutic modalities.

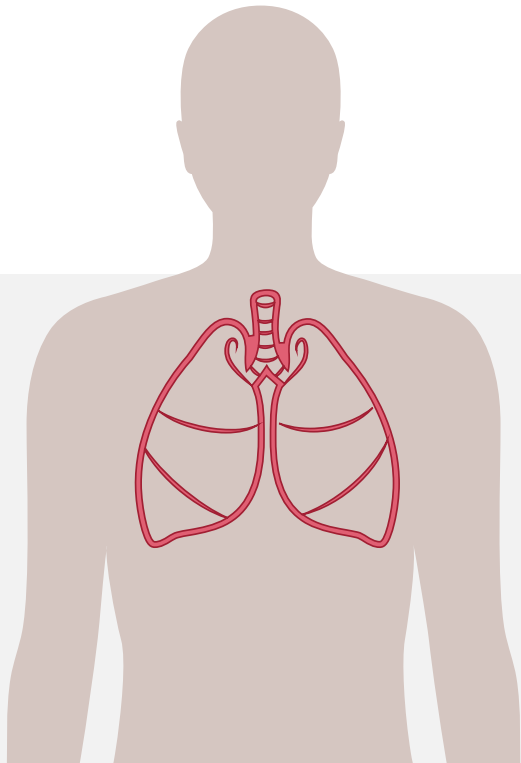
# AMT's Oral Biologic Therapeutics Can Act Locally Along GI Tissue or Enter into Circulation

- 1 Targeting to lamina propria to impact enteric immune system and GI tissue
- 2 Directed to the portal and systemic circulation





# Expanding AMT's Technology Platform: Transformational Therapies in Respiratory Diseases



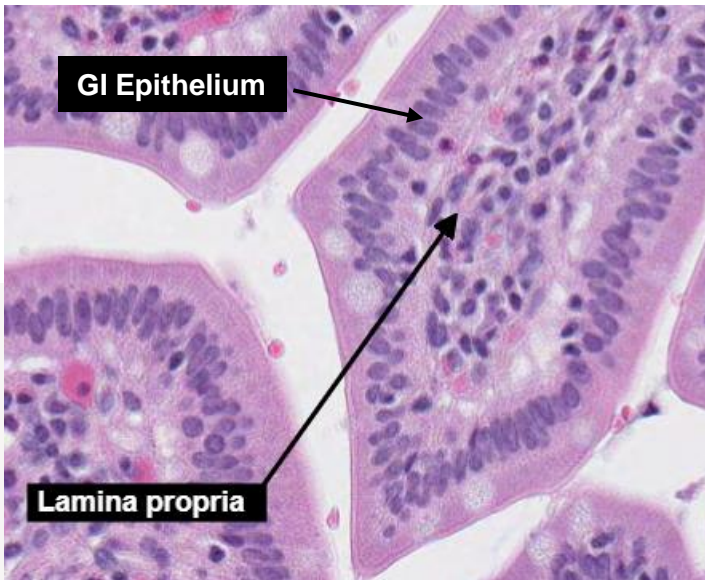
- Pulmonary columnar epithelial cells exhibit transcytosis in a similar manner as intestinal epithelium
- Cells in the pulmonary lamina propria tissue provide a **rich source of novel targets**
- Local, **targeted inhaled biologics** provide a novel opportunity in multiple areas of high unmet medical need

# Similarities of Epithelial Surfaces in the GI & Respiratory Tracts

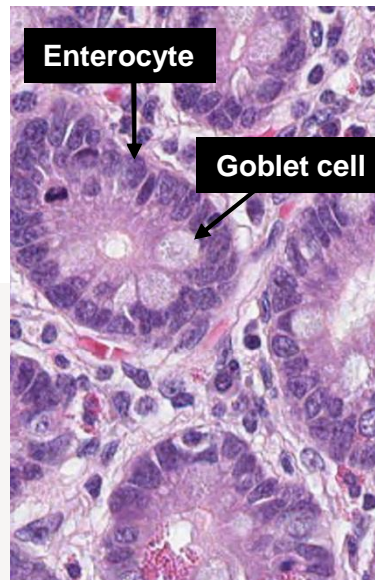
## GI Tract



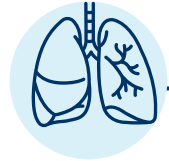
### Mucosa



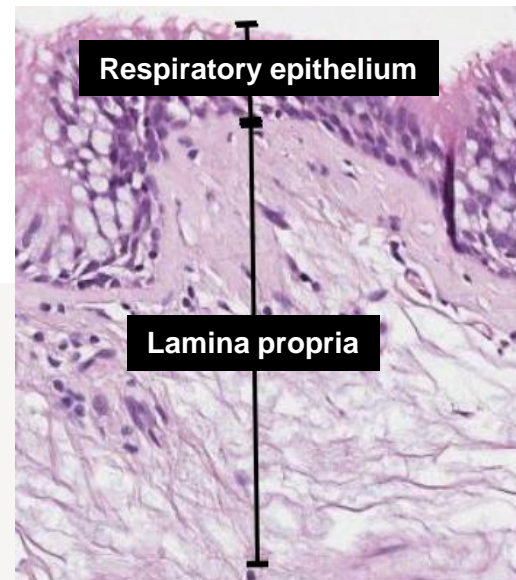
### GI Epithelium



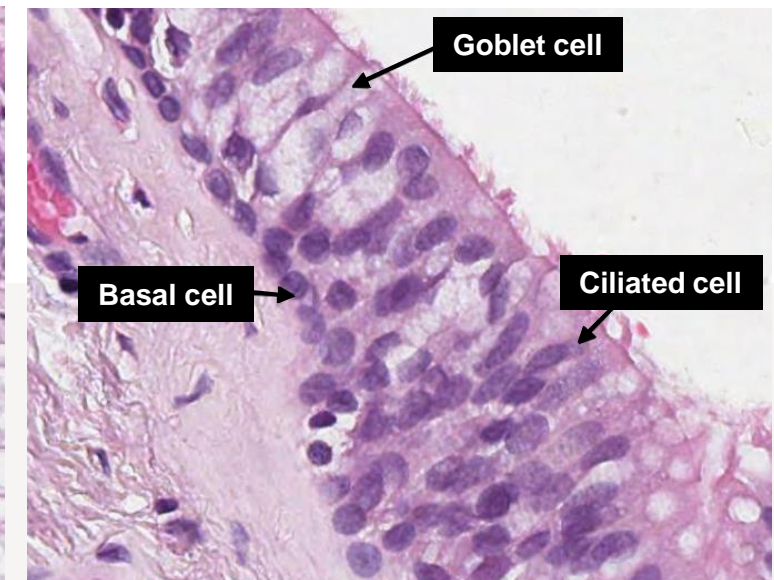
## Respiratory Tract



### Mucosa



### Airway Epithelium

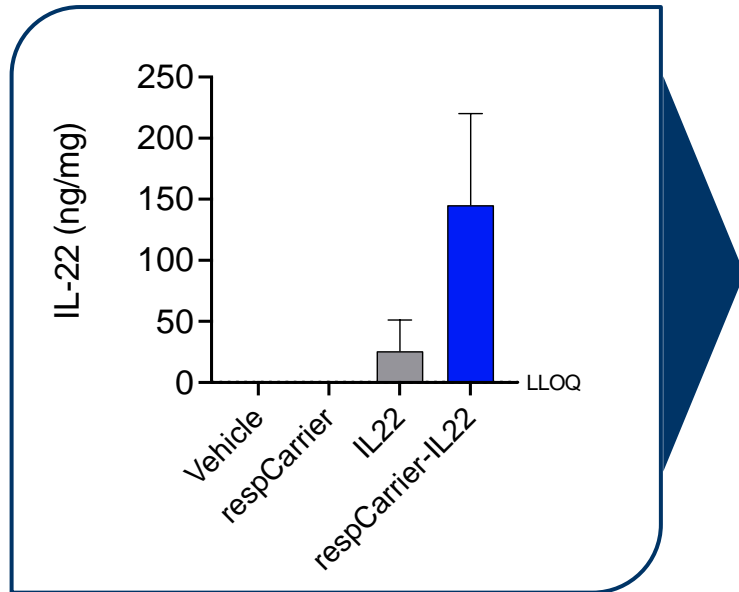


# AMT's respCarrier System Traffics Biologic Therapeutics Across Respiratory Epithelial Barrier In Vivo

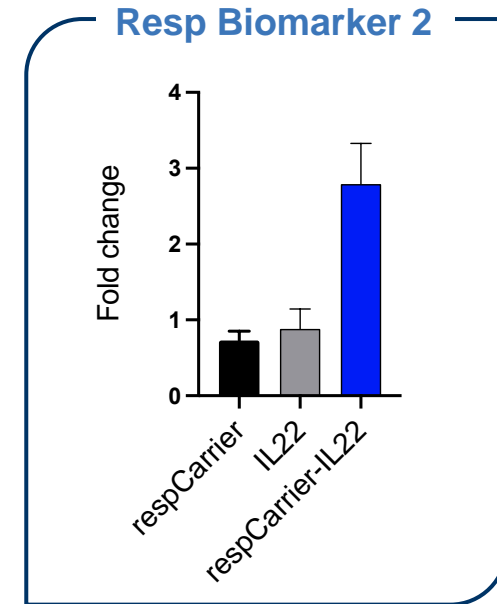
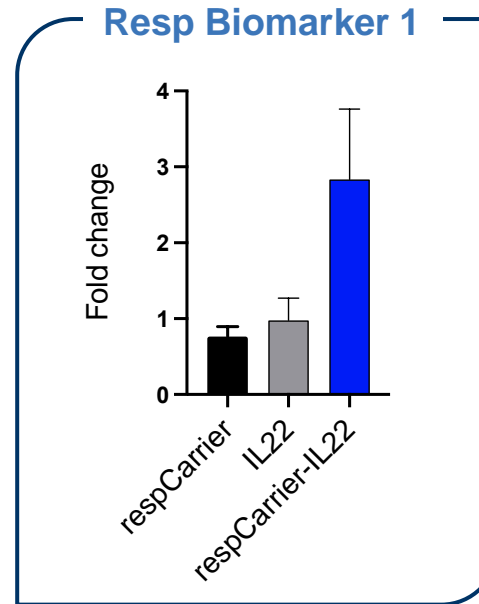
- respCarrier:
  - Based on natural trafficking pathway evolutionarily optimized for respiratory epithelium
  - Distinct carrier from oral (cholix-based) system

*Example: respCarrier-IL22 fusion biologic – lung PK and PD*

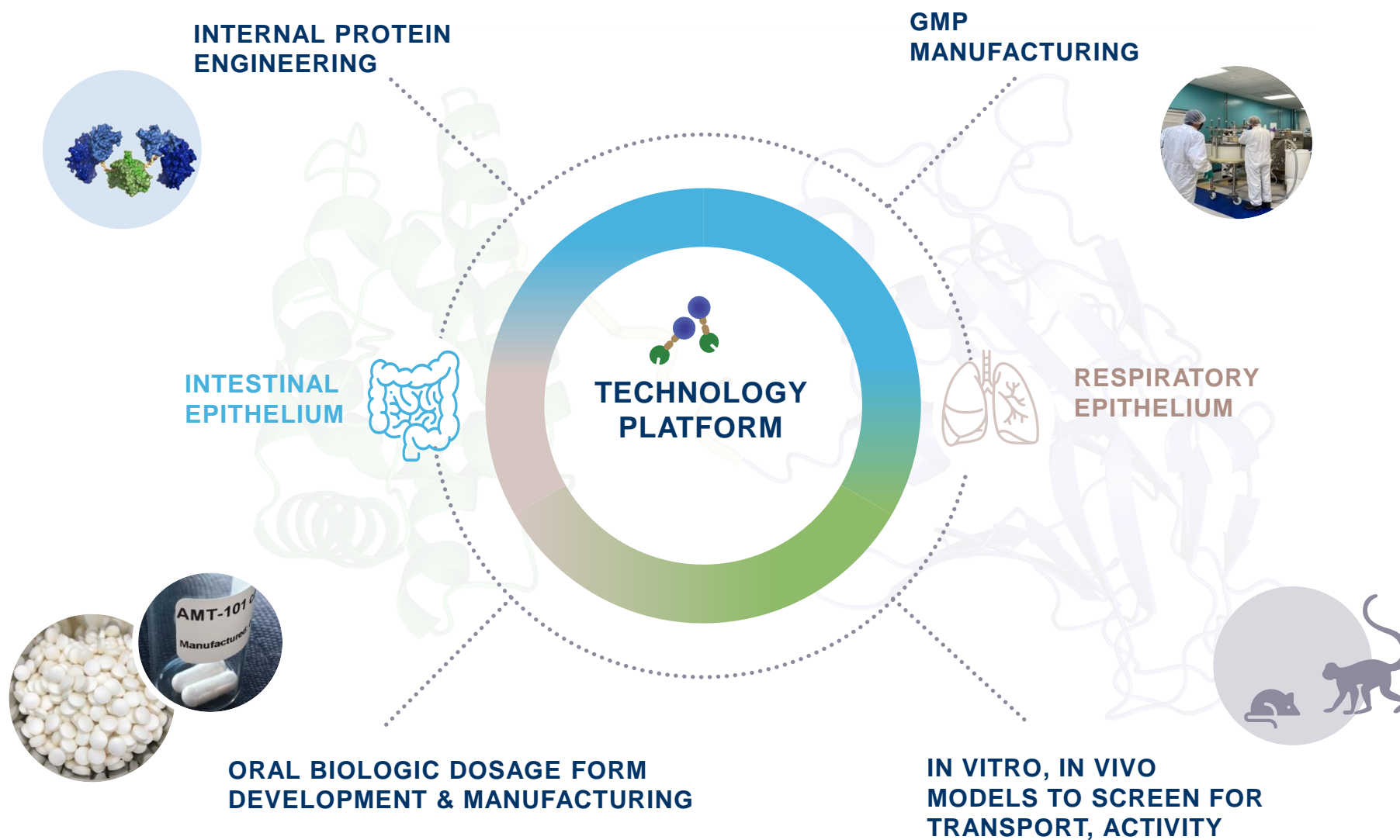
Tissue (lung) PK



Upregulation of Respiratory Tract Barrier Function Genes



# Broad Biologics Platform Enabled by Internal Core Capabilities





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## Clinical Programs

Bittoo Kanwar, MD  
Chief Medical Officer

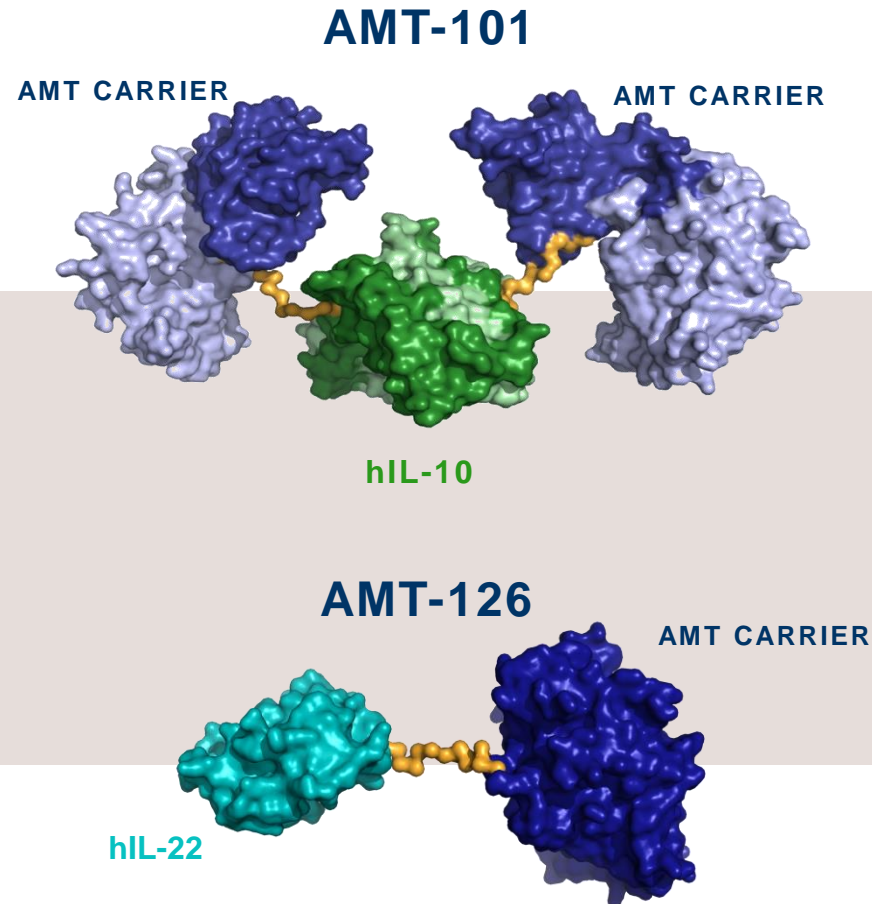
# Two Complementary Oral Product Candidates in the Clinic

## 2 Product candidates in the clinic

**AMT-101** (Oral fusion, IL-10; Four Phase 2 clinical trials)

**AMT-126** (Oral fusion, IL-22; One Phase 1 clinical trial)

## 5 Active global clinical trials



# Distinguished IBD and Rheumatology Key Opinion Leaders



**Peter Lipsky, MD**

*Rheumatology Specialist  
Former Scientific Director and Chief of the Autoimmunity  
Branch, NIAMS, National Institutes of Health*



**Brian Feagan, MD, FRCPC**

*Professor of Medicine, Departments of Medicine, Division  
of Gastroenterology, Epidemiology and Biostatistics  
Western University, Canada*



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# IL-10 and IL-22 Biology

Peter Lipsky, MD

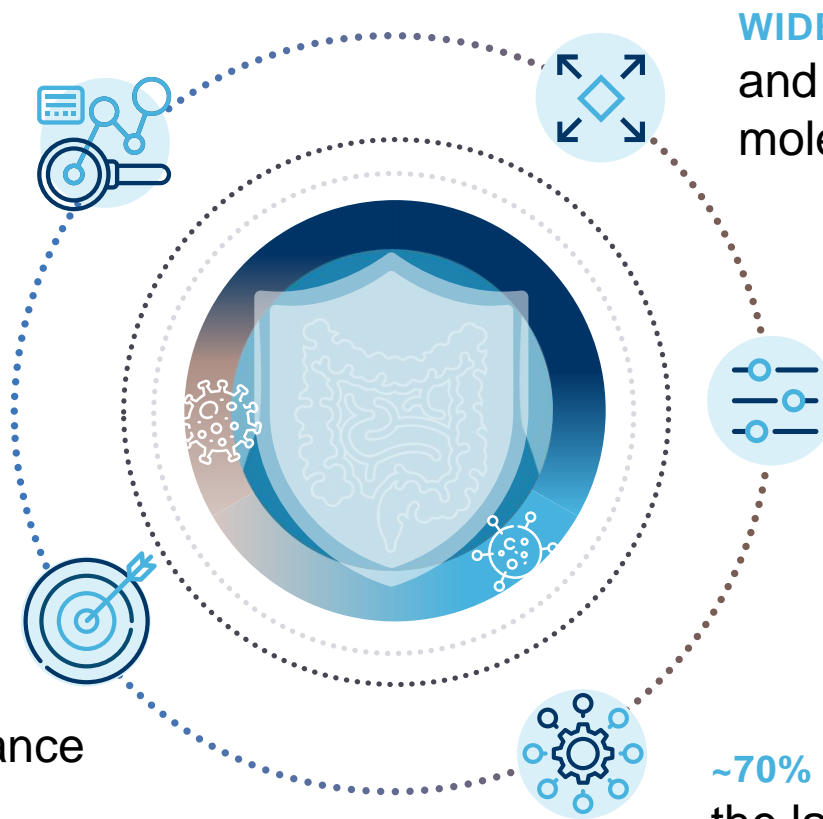


# Critical Role of the Immune System... and its Importance as a Therapeutic Target in the GI Tract

## CONSTANT SURVEILLANCE

Tolerance or effector response:  
cellular differentiation,  
proliferation, circulating  
mediators, and cell trafficking

**TARGETING THE LP** precisely  
accesses the immune surveillance  
system

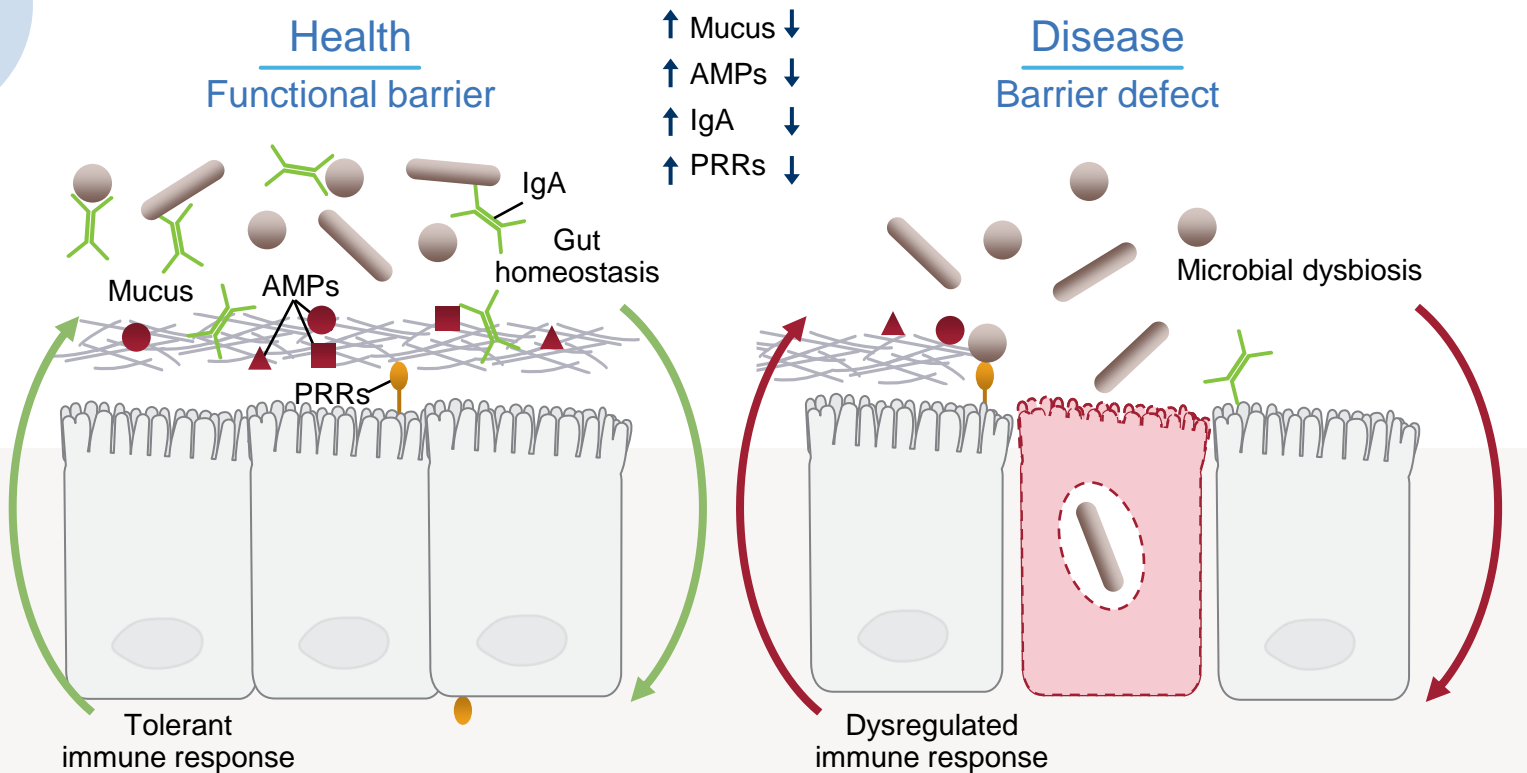


**WIDELY DISTRIBUTED** to have easy  
and early access to incoming  
molecules and organisms

**LEARNS AND REMEMBERS** what  
is dangerous/safe, available  
and working at all times

**~70% OF THE IMMUNE SYSTEM** is in  
the lamina propria (LP), at the  
basal side of the epithelium

# Aberrant Immune Activation and/or Disruption of Mucosal Epithelial Barriers Lead to Local and Systemic Disease



- Loss of epithelial barrier integrity
- Dysregulated immune response
- Microbial dysbiosis
- Mucosal inflammation and tissue destruction

↑ ↑ ↑  
↓ ↓ ↓  
Immune tolerance  
Microbial metabolites  
Cell trafficking

Systemic *pathologies...*

Epithelium ↑ TGF-β, IL-33, TSLP, BAFF, APRIL  
CD103<sup>+</sup> DCs ↑ TGF-β retinoic acid  
T<sub>reg</sub> cells ↑ IL-10, TGF-β  
Roryyt<sup>+</sup> ILCs ↑ IL-22  
Macrophages ↑ IL-10  
B cells ↑ Commensal-specific IgA

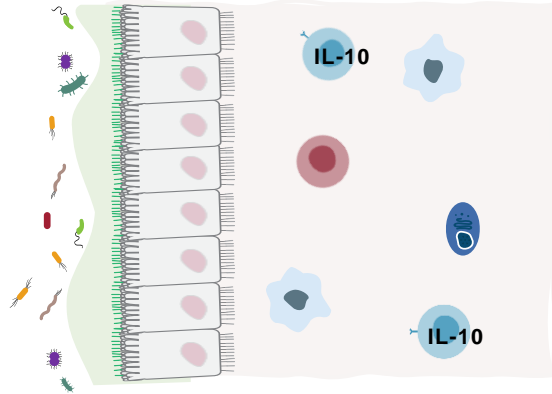
Epithelium ↑ IL-6, IL-1  
DCs ↑ IL-12, IL-23  
T<sub>H</sub>1 cells ↑ IFN-γ  
T-bet<sup>+</sup> ILCs ↑ IFN-γ  
T<sub>H</sub>17 cells ↑ IL-17A  
Macrophages ↑ TNF, IL-12  
B cells ↑ Commensal-specific IgG

Repairing epithelial barrier function and aberrant immune activation can have both local and systemic effects

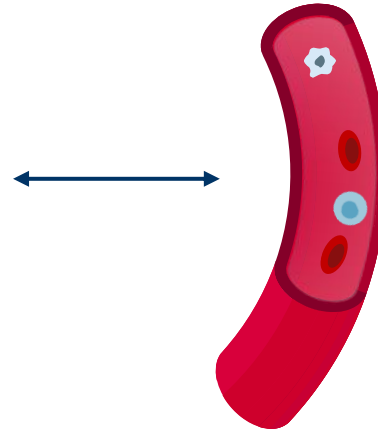
# Immune Dysregulation Can Also Affect Peripheral Locations (e.g., Joint, Skin, Brain)

**'VIRTUOUS  
CYCLE'**

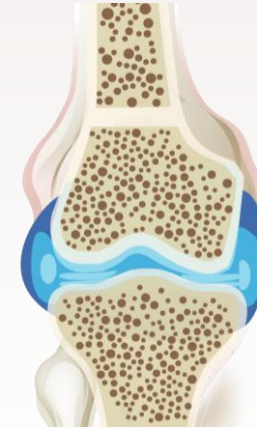
HEALTH  
MICROBIOTA    INTACT GUT  
BARRIER    TOLERANT  
IMMUNE CELLS



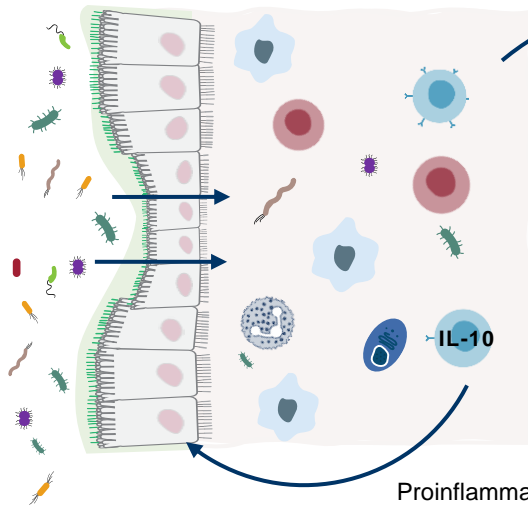
HOMEOSTASIS



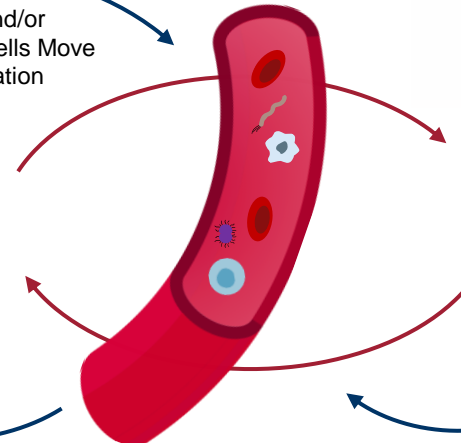
NON-INFLAMED JOINT



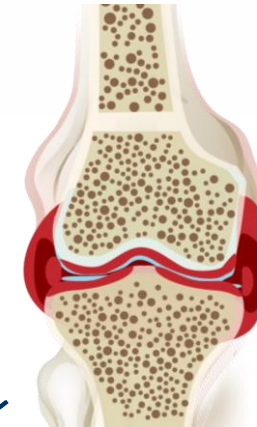
DYSBIOSIS    DAMAGED GUT  
BARRIER    ACTIVATED  
IMMUNE CELLS



INFLAMMATORY  
FEEDFORWARD LOOP



INFLAMED JOINT

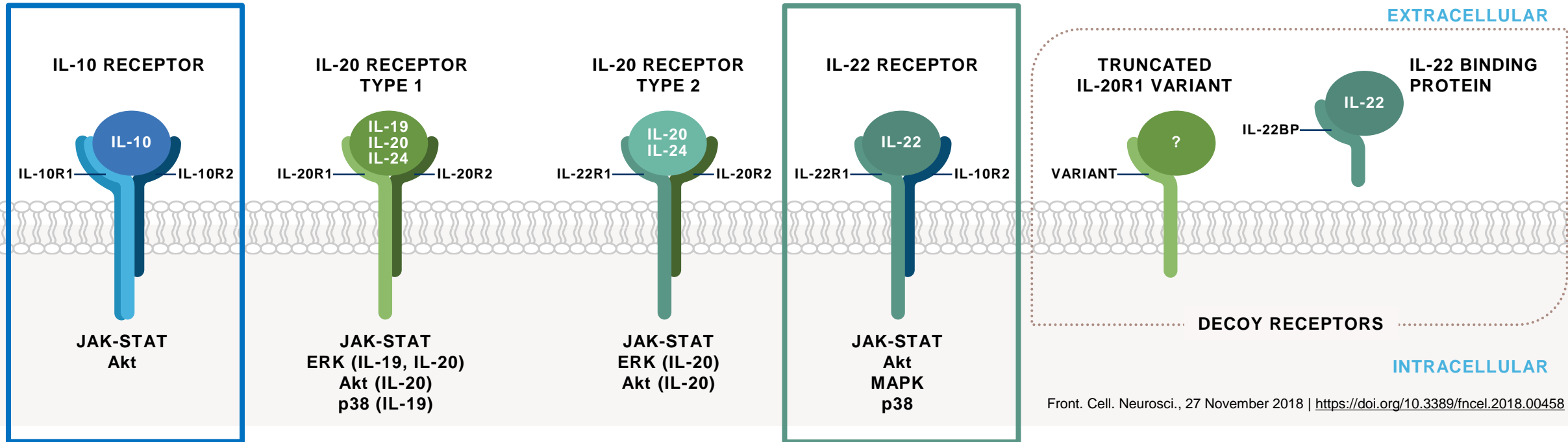


Proinflammatory Reactions  
Leading to Epithelial Damage  
and Intestinal Permeability

Inflammatory cells  
home to the intestine

# Role of IL-10 and IL-22 in the Immune System

IL-10 and IL-22 are Members of the Larger IL-10 Family and Share a Receptor Component



## IL-10

- Maintains immune homeostasis
- Bridges innate and adaptive immune system cells

## IL-22

- Maintains epithelial barrier function
- Regulates microbiome



# Clinical Consequences of Low or Absent IL-10

## IL-10 KO Mice or IL-10 Receptor Mutations

- Spontaneous development of colitis essentially irrespective of background, though severity varies
- Disease expression varies with microbiome

## Humans- IL-10 Deficiency and IL-10R Loss of Function Mutations

- Early onset/pediatric IBD, severe and intractable, fistula formation, perianal disease

<https://doi.org/10.1016/j.jaci.2012.09.025>

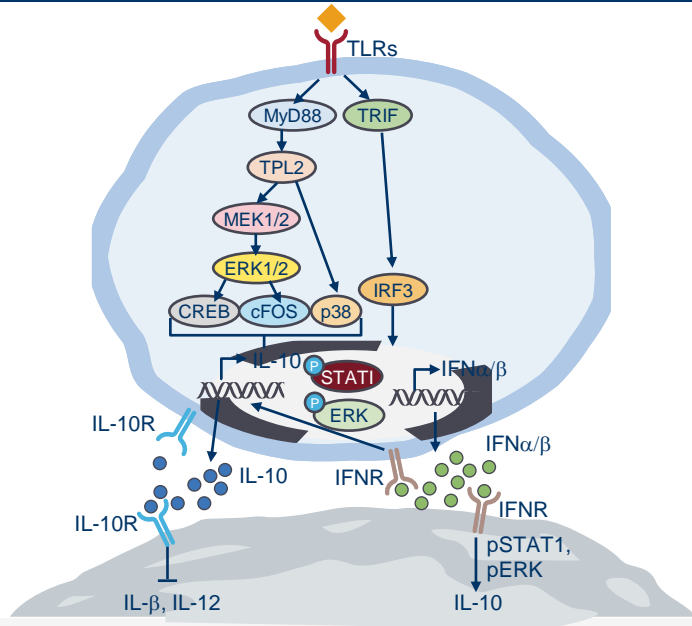
## Immunomodulation Induced by IL-10 has Demonstrated Improvement in Arthritis in Animals and RA Patients

- Systemic administration of IL-10 associated with AE's

EW St. Clair Rheum 1999 38:293-297

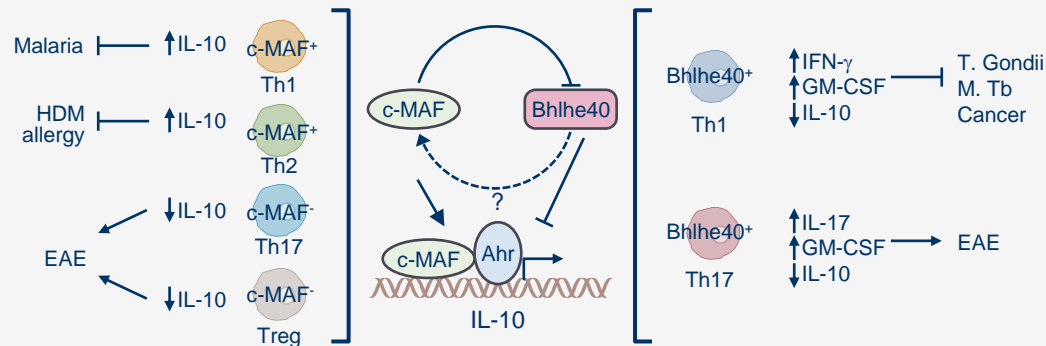
Maini et al: Arthr Rheum 40 suppl 9 S224 1997

# Regulation of IL-10 Expression in Myeloid Cells and T Cells



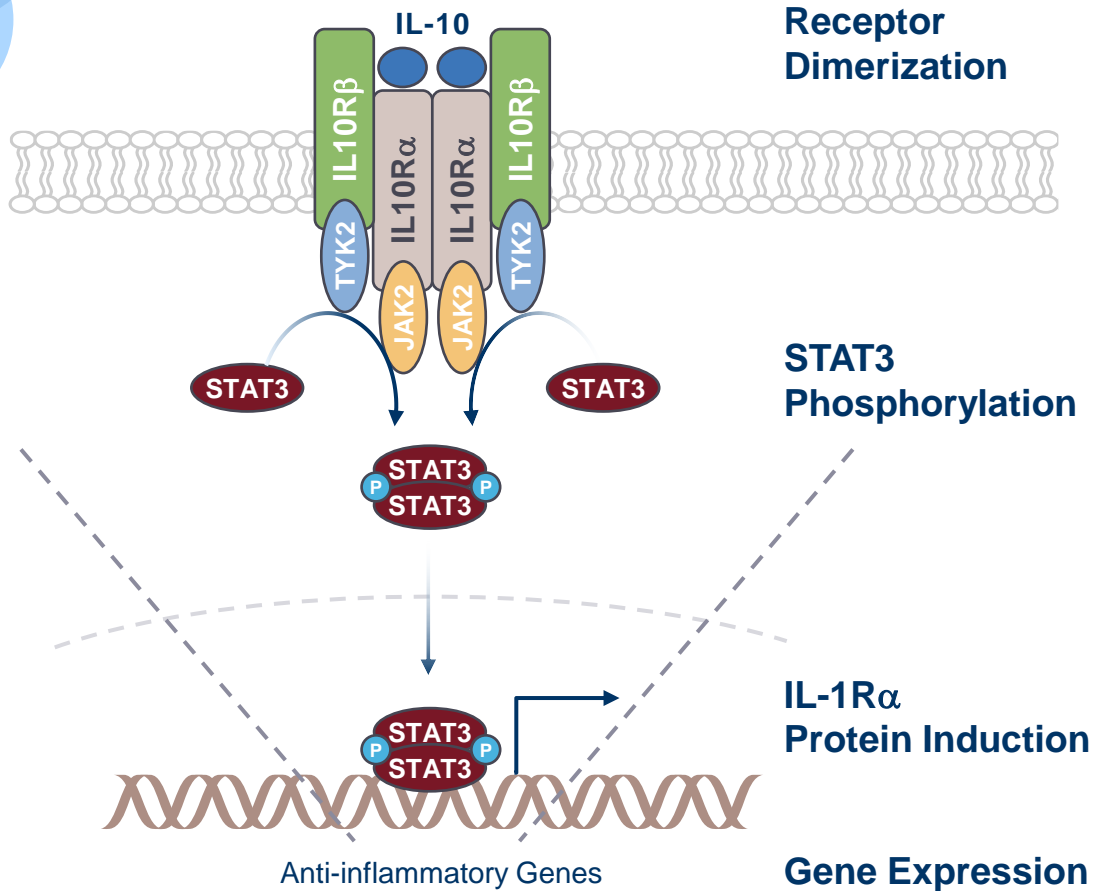
IL-10 and Type 1 IFNs are induced in myeloid via several different pathways; TLR engagement and signaling through TLR2-MSK-CREB, and TPL-2-ERK.

Type 1 IFNs also induce IL-10 production and work synergistically with IL-10 to regulate downstream inflammatory responses.



IL-10 expression in T cells is highly regulated with cMAF increasing IL-10 in various Th cells and Bhlhe40 repressing IL-10 in Th1 and Th17 cells. Of note, cMaf and Bhlhe40 may negatively regulate the expression of one another.

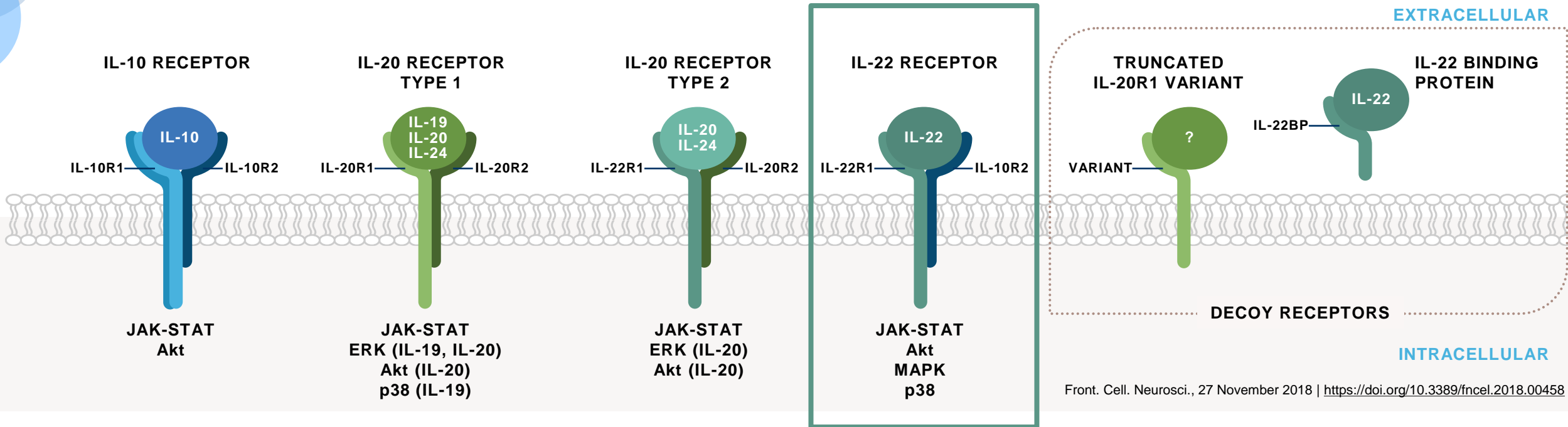
# IL-10 Functions and Mechanism of Action



- Deactivates inflammatory macrophages
- Decreases APC- and T cell produced cytokines
- Suppresses T cell proliferation and inflammation
- Promotes tolerogenic dendritic cells → T regulatory cell development (Tr1)
- Role for IL-10 in the **NLRP3 pathway**: Inhibits **inflammasome**-mediated caspase 1 activation
  - Important player in the control of sterile inflammation

# Role of IL-10 and IL-22 in the Immune System

IL-10 and IL-22 are Members of the Larger IL-10 Family and Share a Receptor Component



## IL-10

- Maintains immune homeostasis
- Bridges innate and adaptive immune system cells

## IL-22

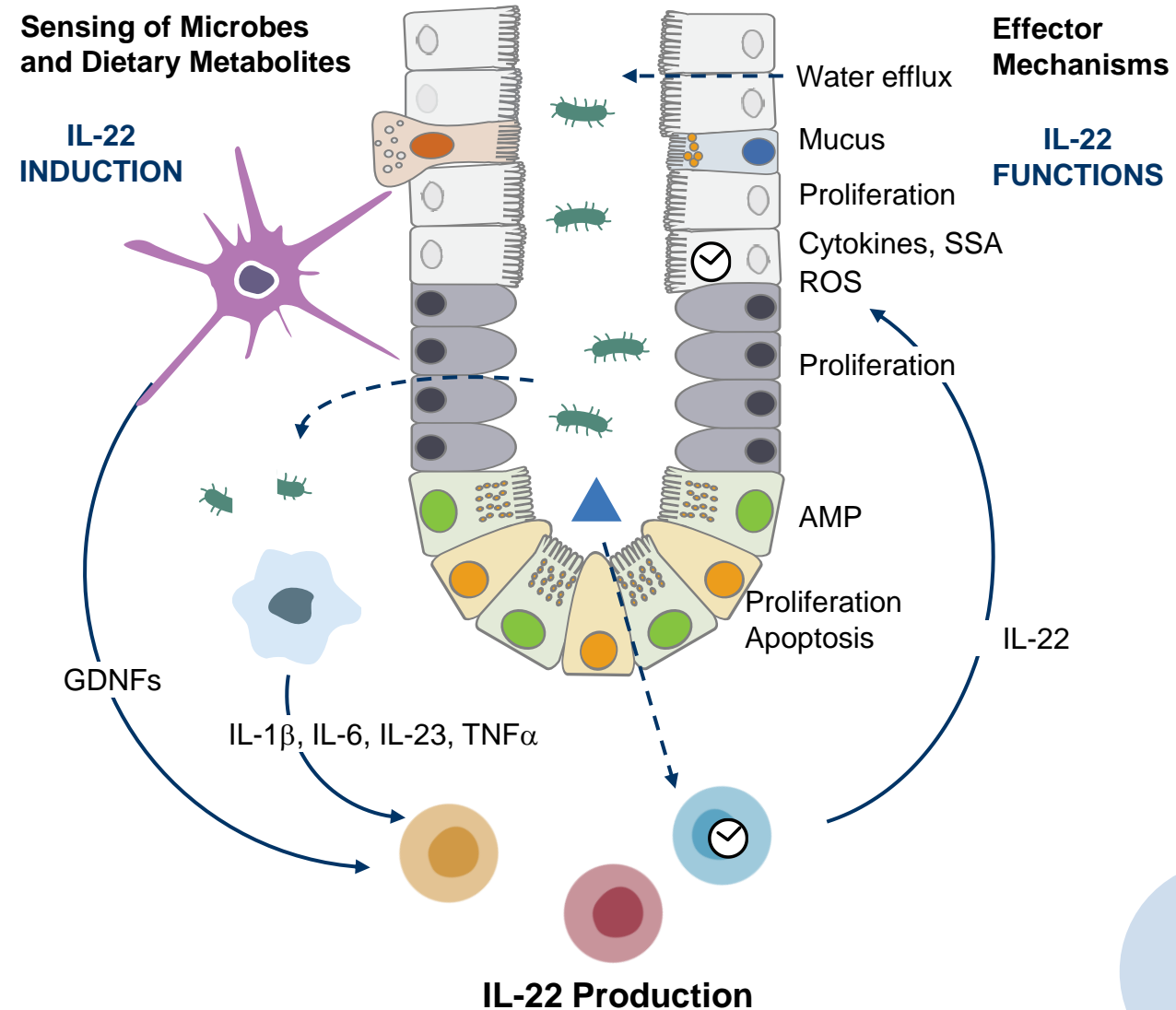
- Maintains epithelial barrier function
- Regulates microbiome



# IL-22 Promotes a Healthy Epithelial Barrier

## Roles of IL-22

- Restores epithelial barrier integrity and homeostasis
- Promotes cell proliferation and supports mucosal healing
- Regulates microbiome via mucins and antimicrobial peptides



# Endogenous Cytokines and Validated Therapeutic Targets: IL-10 and IL-22 Play Critical Roles in Immune Homeostasis and Disease

## IL-10



**Net positive effect is to restore immune homeostasis and reduce inflammation**

- Re-establish homeostasis
- Enable local repair processes
- Decrease inflammation
- Reduce local induction of inflammatory mediators that can act at a distance
- Reduce trafficking of proinflammatory cells
- Naturally occurring endogenous cytokines

## IL-22



**Net positive effect is to reduce ingress of microbial antigens and organisms, reduced inflammatory response, local repair**

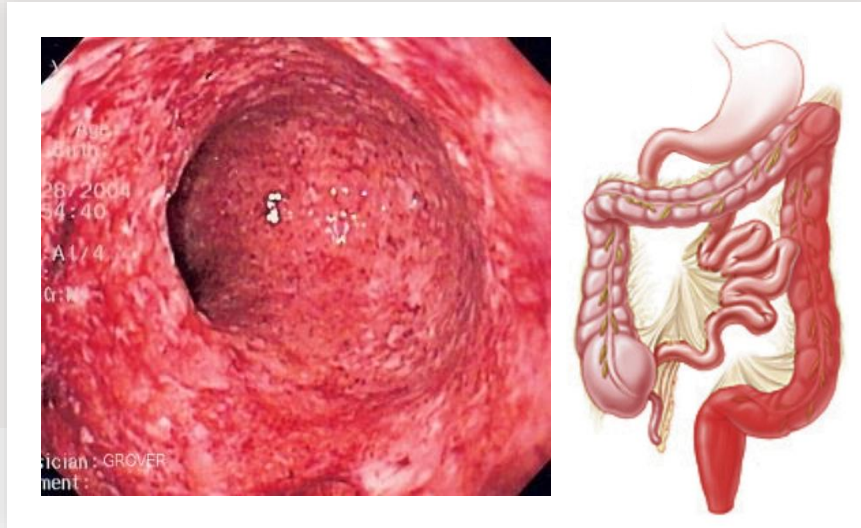
- Strengthen tight junctions and reduce gut leakiness
- Induce endogenous antimicrobial peptides and reduce dysbiosis
- Induction of mucins to restore barrier function at epithelial surface
- Naturally occurring endogenous cytokines

# Treatment Landscape in IBD

Brian Feagan, MD, FRCPC

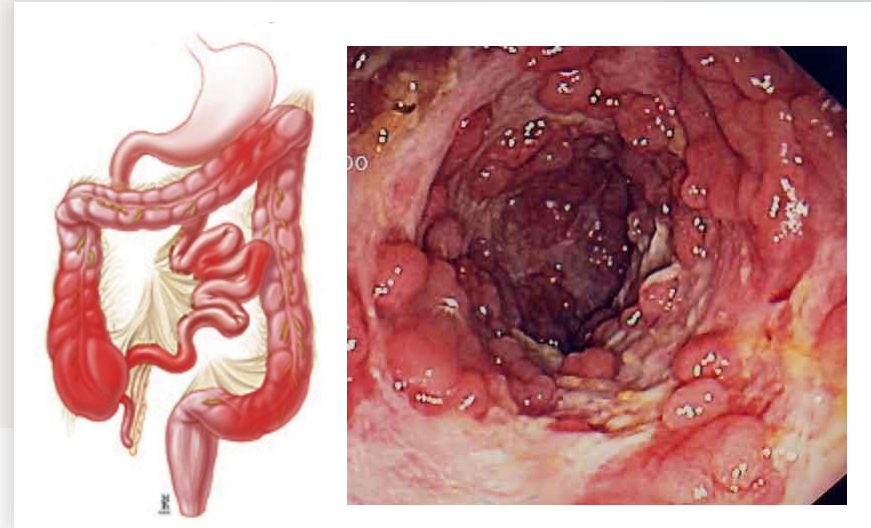
# Inflammatory Bowel Disease (IBD)

## Ulcerative Colitis



- Limited to colon
- 50% mod/severe disease
- Increased risk of CRC

## Crohn's Disease



- Any region of GI tract
- 30% limited to terminal ileum
- 70% require surgery



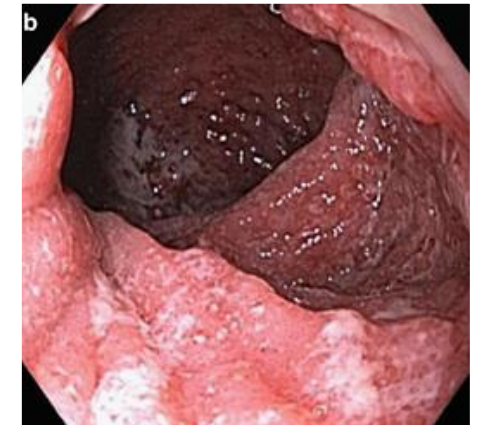
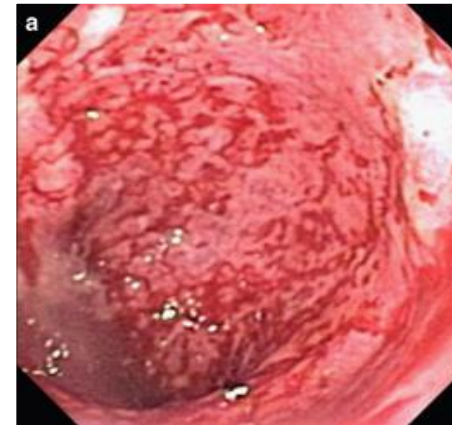
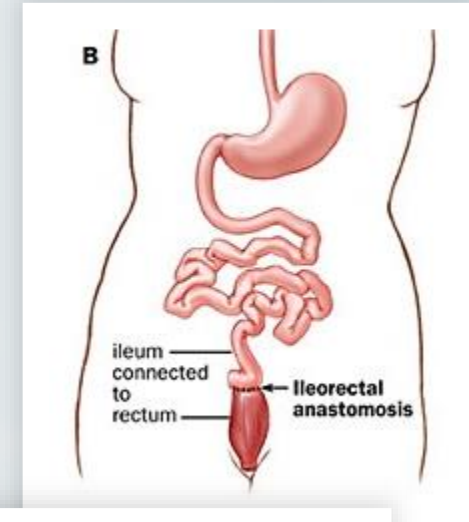
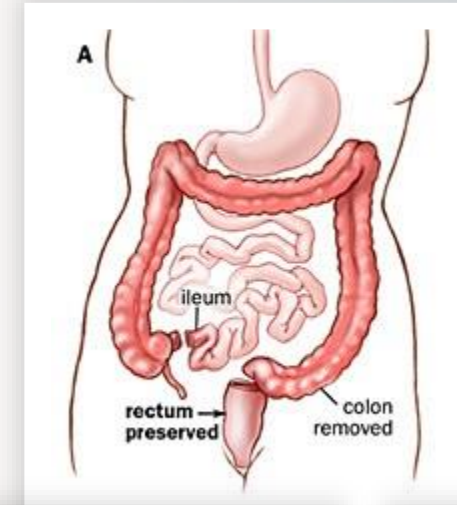
# Pouchitis - Ileal Pouch Anal Anastomosis (IPPA)

## Prevalence

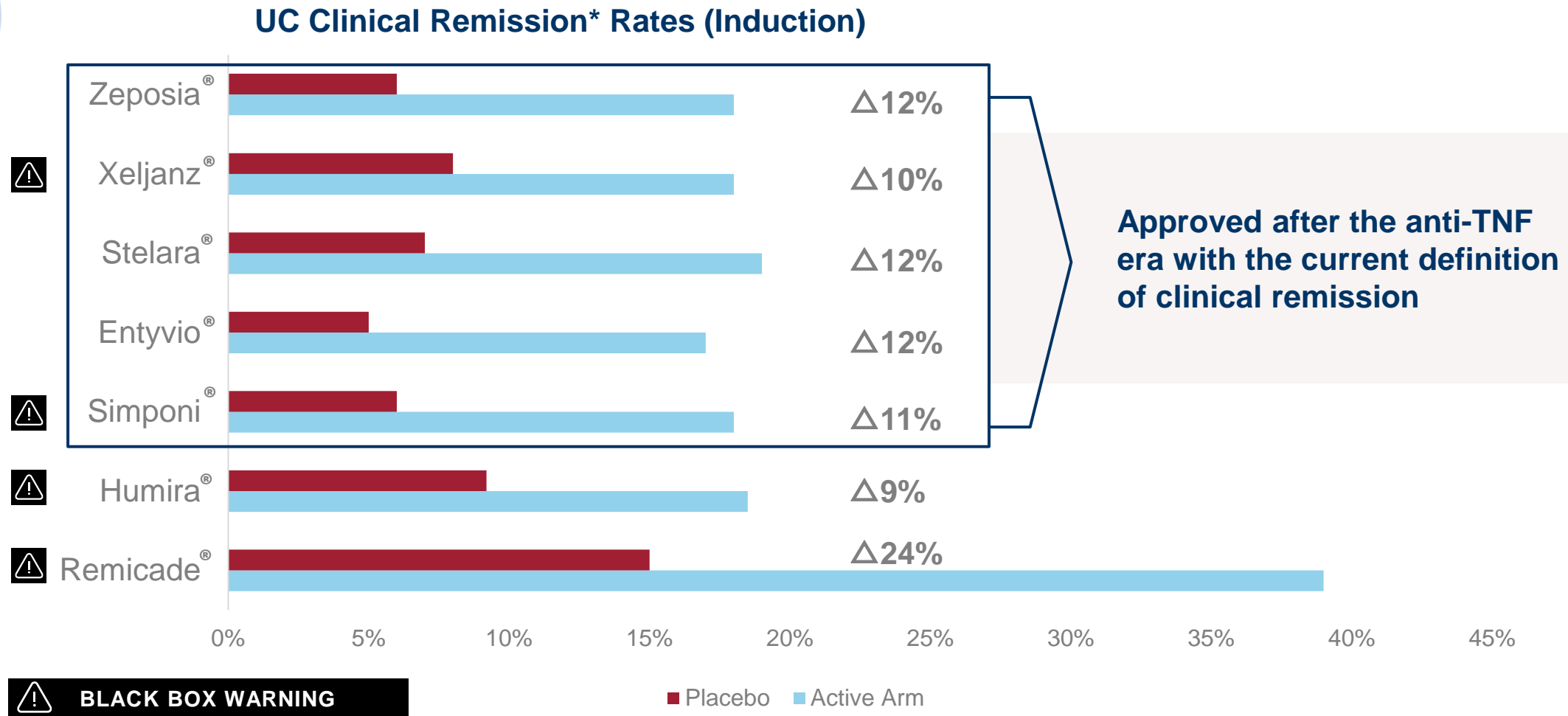
- Up to 30% of UC patients will require colectomy at some point
- Majority will have an ileal pouch anal anastomosis (IPAA)
- 50% will develop at least one episode of pouchitis within 10 years
- 25% of those will develop chronic pouchitis

## Epidemiology

- 20-40K in US & EU (each)
- Orphan population with no approved therapies



# UC Monotherapy Rates of Remission Are Sub-Optimal with Current Approved Therapies and Have Safety Concerns



\*Clinical Remission defined as as Mayo score  $\leq 2$  with no individual subscores  $> 1$  for Remicade, Humira, Simponi, Entyvio, Stelara, and Xeljanz. For Zeposia, Clinical Remission defined as rectal bleeding subscore = 0, stool frequency subscore = 0 or 1 (and a decrease from baseline in the stool frequency subscore of  $\geq 1$  point), and endoscopy subscore = 0 or 1 without friability.

# Clinical Decision-Making Strategy to Enable Remission: Significant Unmet Needs in IBD Development

Complementarity for Additive Benefit

Synergy for Multiplicative Effects

## Start with Simplest Rx

- New patients, biologic naive patients, patients failing a biologic
- Seeking clinical remission, adherence, QoL, safety, durable response

## Proceed to Combo Rx

- Add new MoA to enhance response
- Safe, convenient
- Unlike other combos, doesn't carry added toxicity

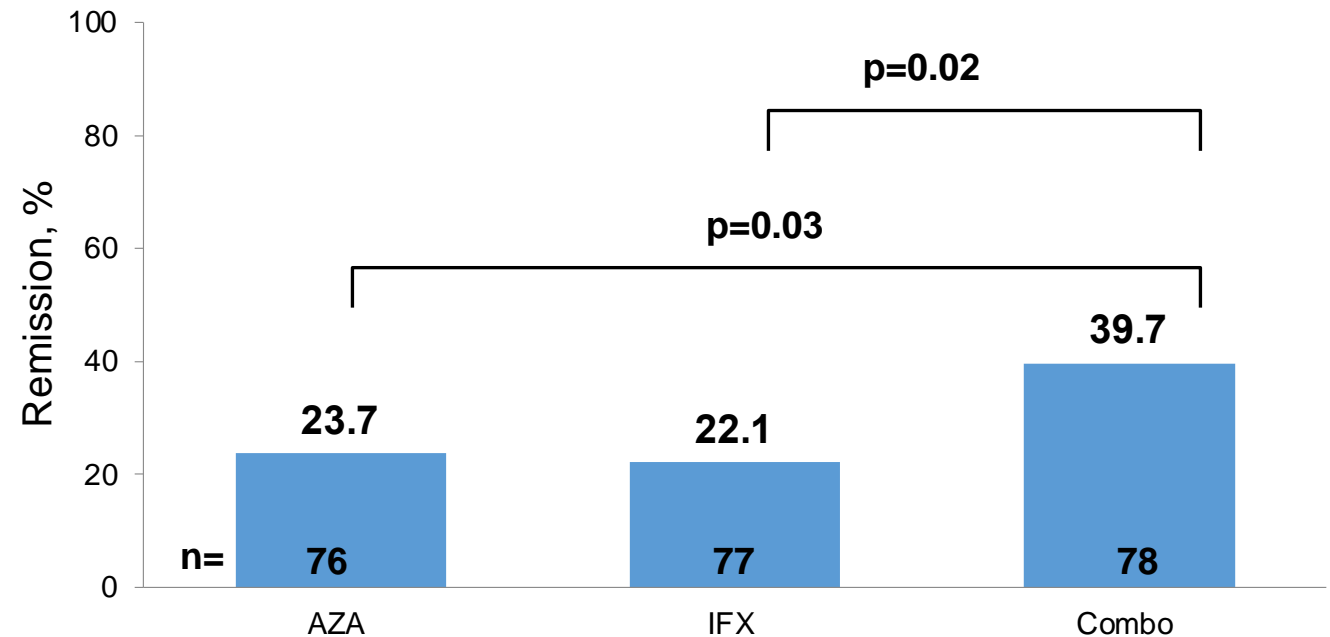
## Synergistic Combo Rx

- Literature: TNF- $\alpha$  responses lower in patients with low IL-10
- Safe, convenient
- Unlike other combos, doesn't carry added toxicity

# Combination Treatment Regimens Have Demonstrated Improved Efficacy Along with Safety Concerns

## Infliximab + Azathioprine

- Randomized, double-blind study
- Mayo score of 6–12 at baseline
- AZA/TNF-naïve population
- Primary endpoint: corticosteroid-free remission at Week 16
- Increased rate of serious infections and lymphoma observed with combination therapy



# AMT-101 Phase 2: Key IBD Endpoints

AMT-101 Phase 2 trials have been designed with comprehensive and state-of-the-art endpoints

- Enables clear signal detection and decision making for pivotal trials

## Mayo Score (3-Component)

- Current definition of clinical remission (endoscopic and stool frequency sub score of 0/1 and rectal bleeding sub score of 0)

## Importance of UC-100 Endpoint

- 100-point composite scale incorporating stool frequency, endoscopy, and histology
- Designed to optimize treatment effect in early phase/smaller trials for efficient development



# UC Mayo Clinic Scoring System (Previous Definition of Remission)

Score	Mucosal Appearance at Endoscopy	Rectal Bleeding	Stool Frequency	Physician Rating of Disease Severity
0	Normal/ inactive disease	No blood with bowel movements	Normal number of stools/day	Normal
1	Mild disease (erythema)	Blood <50% of time	1–2 > normal/day	Mild
2	Moderate disease (ulcers/friable)	Blood >50% of time	3–4 > normal/day	Moderate
3	Severe disease (active bleeding)	Passing blood alone	>4 > normal/day	Severe

- Moderate to Severely active disease defined as a score of 6-12
- Remission defined as a score  $\geq 2$

# Current UC Definition of Remission (Key Topline Efficacy Readout in AMT-101 Phase 2 UC Trials)

**(1°Endpoint):**  
Endoscopic Score  $\leq 1$   
+  
Stool Frequency  
Score  $\leq 1$   
(with 1+ pt reduction)  
+  
Rectal Bleeding  
Score 0

Mucosal Appearance at Endoscopy	Rectal Bleeding	Stool Frequency	Physician Rating of Disease Severity
Normal/ inactive disease	No blood with bowel movements	Normal number of stools/day	Normal
Mild disease (erythema)	Blood <50% of time	1–2 > normal/day	Mild
Moderate disease (ulcers/friable)	Blood >50% of time	3–4 > normal/day	Moderate
Severe disease (active bleeding)	Passing blood alone	>4 > normal/day	Severe

Physician Rating not part of the primary endpoint

APPLIED | MOLECULAR | TRANSPORT

# Oral AMT-101 Overview

Bittoo Kanwar, MD  
Chief Medical Officer

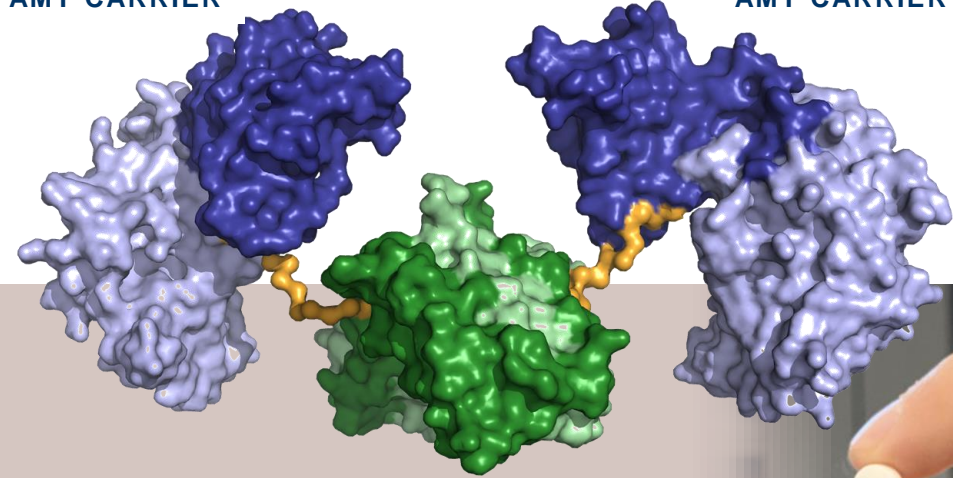
# AMT-101

- Oral, GI-selective once-daily biologic
- Unique product profile with potential use as single agent or in combination
- Ongoing comprehensive Phase 2 program in multiple UC populations and RA

## Oral IL-10 Fusion Biologic

AMT CARRIER

AMT CARRIER



hIL-10



 *The Journal of*  
**Immunology**

**A Novel Fusion of IL-10 Engineered to Traffic across Intestinal Epithelium to Treat Colitis**

Nicole C. Fay, Baby-Periyannayagi Muthusamy, Linh P. Nyugen, Radhika C. Desai, Alistair Taverner, Julia MacKay, et al

# Interleukin-10 (IL-10): A Clinically-Validated Inflammation Target

Clinical efficacy in IBD with systemic rhIL-10  
(SAEs: anemia and thrombocytopenia due to systemic  
administration)



## IL-10 and Macrophages Orchestrate Gut Homeostasis

Alberto Mantovani<sup>1,\*</sup> and Federica Marchesi<sup>1</sup>

<sup>1</sup>Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano, Italy, and Department of Biotechnologies and Translational Medicine, University of Milan, 20122 Milan, Italy

\*Correspondence: [alberto.mantovani@humanitasresearch.it](mailto:alberto.mantovani@humanitasresearch.it)  
<http://dx.doi.org/10.1016/j.immuni.2014.04.015>

JOURNAL OF IMMUNOLOGY

### BRIEF REVIEWS

#### IL-10: The Master Regulator of Immunity to Infection

Kevin N. Couper, Daniel G. Blount,<sup>1</sup> and Eleanor M. Riley<sup>2</sup>

Gut Inflammatory bowel disease

### ORIGINAL ARTICLE

#### Anti-TNF therapy in IBD exerts its therapeutic effect through macrophage IL-10 signalling

#### Safety and Efficacy of Recombinant Human Interleukin 10 in Chronic Active Crohn's Disease

STEFAN SCHREIBER,\* RICHARD N. FEDORAK,<sup>†</sup> OLE HAAGEN NIELSEN,<sup>§</sup> GARY WILD,<sup>||</sup>

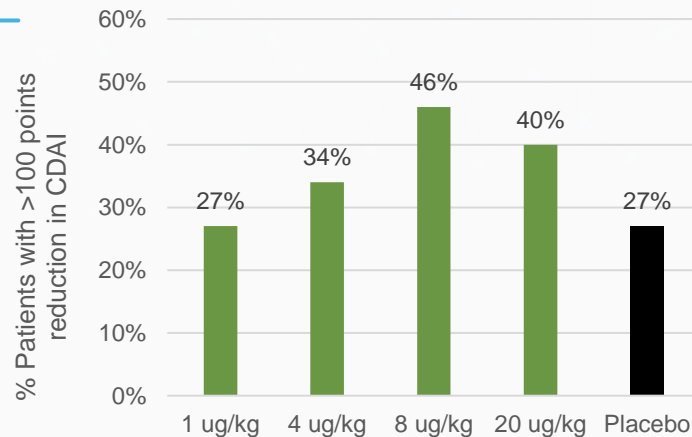


# Interleukin-10 is a Clinically Validated Target Limited by Parenteral Toxicity

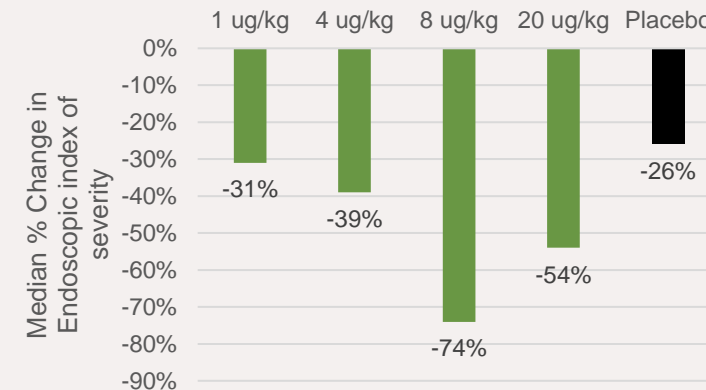
## Prior Clinical Trial (2000) in Moderate-to-Severe Crohn's Disease Patients

- N=329 patients, 28 consecutive days of dosing with rhIL-10 or placebo via sub-Q injection
- 45 patients discontinued due to AEs
- Limiting toxicities (anemia and thrombocytopenia) **observed at all doses** due to systemic exposure/PK
- Systemically administered recombinant human IL-10 shows bell-shaped dose-response curve

### CDAI



### CDEIS



# Completed Successful Phase 1a/b Trial for AMT-101



## Phase 1a HV SAD

AMT-101 was well-tolerated in all doses with no differences in TEAEs observed between active and placebo



## Phase 1b UC MAD

- Adults with Active UC
- Baseline mean Mayo score 7.2
- 14-day treatment period
- 4 dose levels: 1, 3, 10, 30 mg
- Placebo-controlled 3:1



*Multiple Ascending Dose*

**16 UC Patients**

Trends of improvement in objective measures of disease activity including fecal calprotectin, CRP, central read histology in only 14 days of treatment

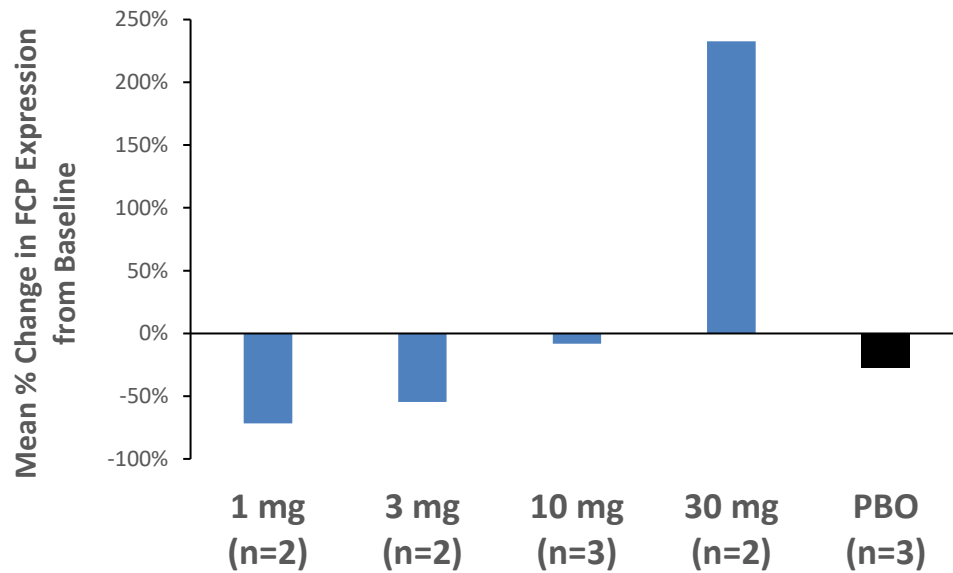
No IL-10 related AEs as previously seen with systemic administration

Informed Phase 2 dose selection at **3mg** and **10mg**

Confirmed no systemic PK by design

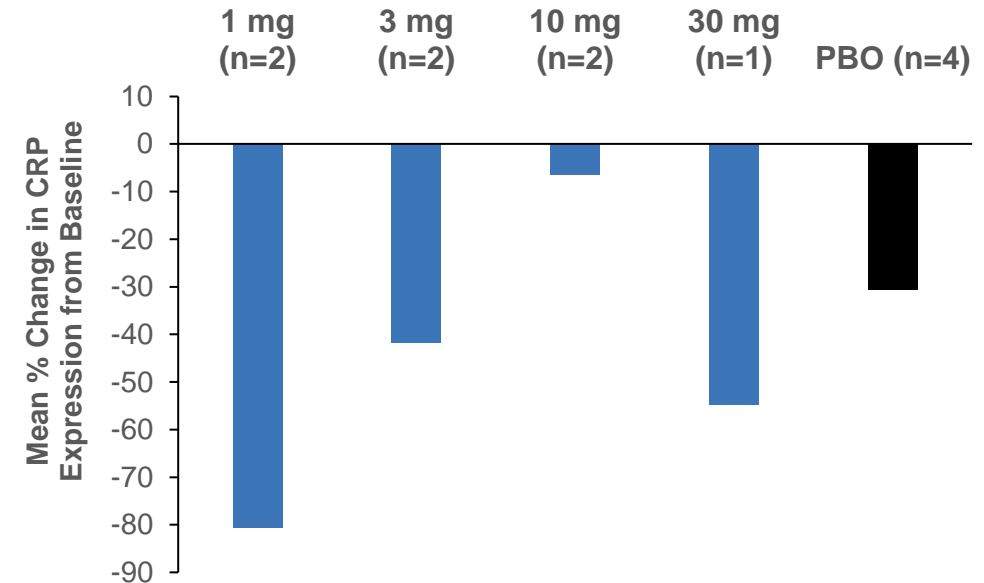
# Changes in Fecal Calprotectin (FCP) and C-Reactive Protein (CRP) Were Observed After 14 Days of Oral Treatment with AMT-101

## Patients with Baseline FCP > 150 ug/g



Placebo adjusted mean reductions of **44%** and **27%** in the 1 mg and 3 mg dose groups

## Patients with Baseline CRP > 5mg/L



Local gut delivery of IL-10 may result in **localized** as well as **systemic** immunomodulatory effects

# Histopathology Improvement in UC Patients After 14 Days of Treatment with AMT-101

Blinded central read

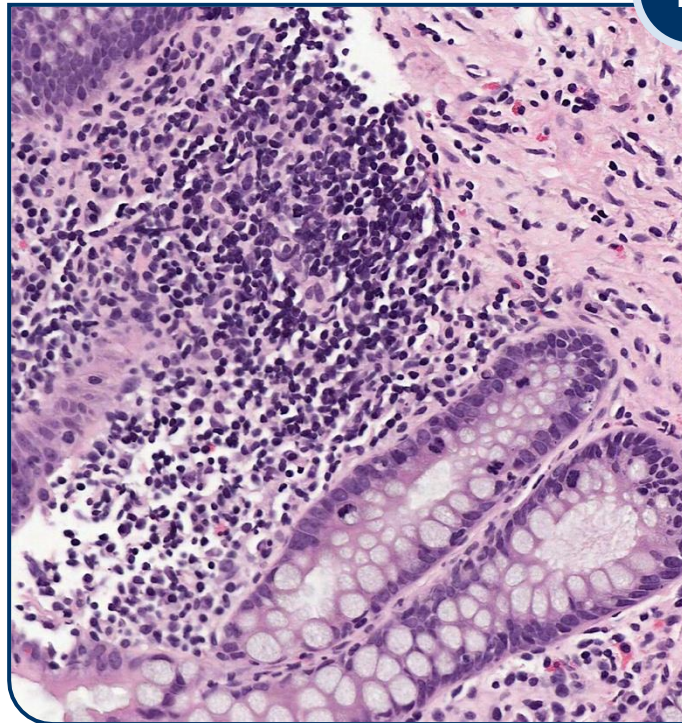
**AMT-101**

**60% (6/10)** of patients on active showed a reduction in total Geboes score

**PLACEBO**

**0% (0/2)** of patients had a reduction in total Geboes score

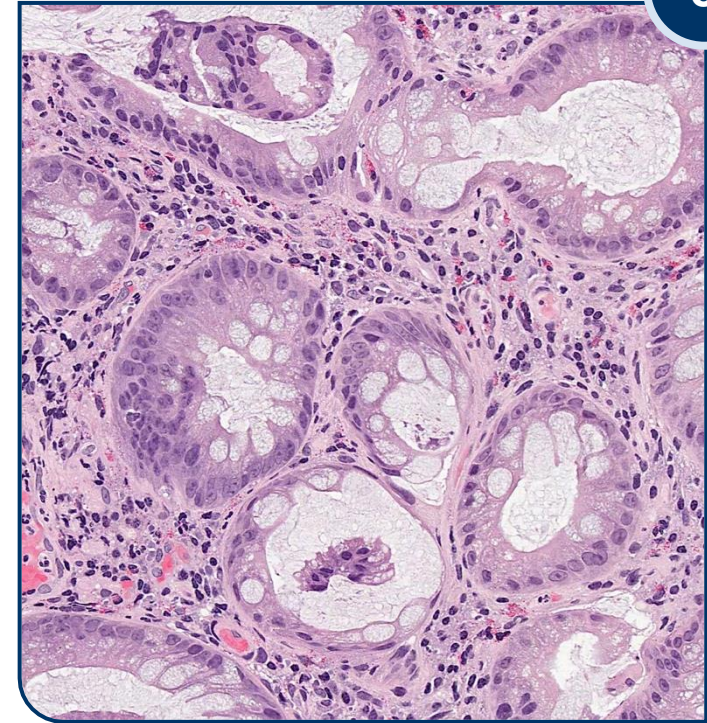
Baseline



15

Geboes score

AMT-101 for 14 days



3

Geboes score

Images: 10 mg dose patient

Geboes score<sup>1</sup>: 0 (normal) to 22 point scale.

<sup>1</sup>B. Lemmens, et al. May 2013.



# Microbiome Improvement Observed in AMT-101 Treatment Groups in UC Patients

Certain species (such as *F. prausnitzii*) ferment dietary fiber into metabolites (e.g. butyrate) that are associated with IL-10 production, immune stasis, and improved gut health <sup>1</sup>

AP&T Alimentary Pharmacology and Therapeutics

Colonisation by *Faecalibacterium prausnitzii* and maintenance of clinical remission in patients with ulcerative colitis

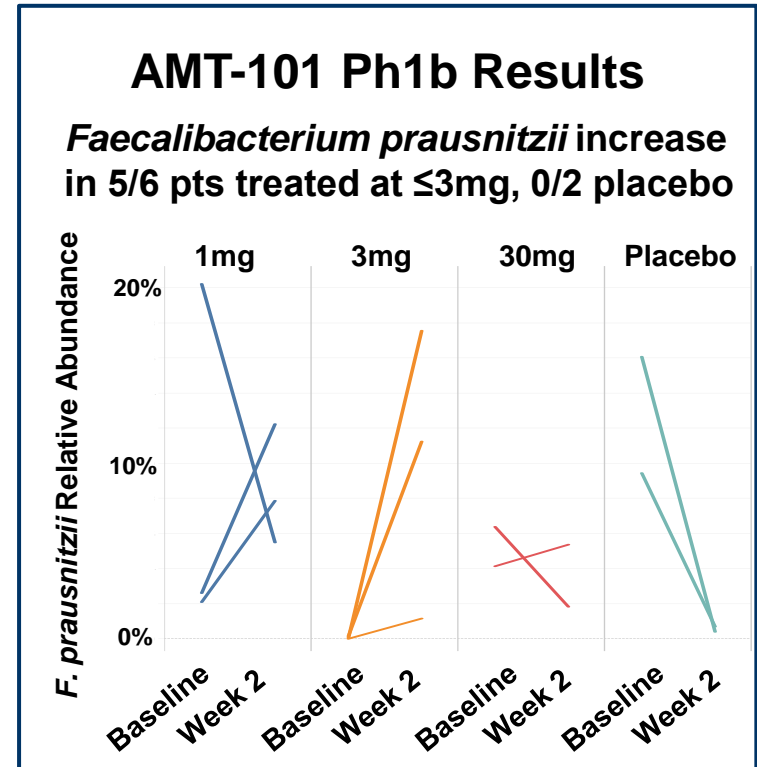
E. Varela, C. Manichanh, M. Gallart, A. Torrejón, N. Borrueal, F. Casellas, F. Guarner & M. Antolin

## Analysis of Phase 1b with active UC patients

Shotgun sequencing for species-level resolution was conducted on baseline and end of treatment stool samples

Changes to gut microbiome observed with lower doses of AMT-101 (1mg and 3mg cohorts):

- Increase in 'beneficial' species belonging to the Firmicutes phyla (e.g. *F. prausnitzii*)
- Observe similar increases to Bacteroidetes; decreases in Actinobacteria



# Totally of Oral AMT-101 Data to Date are Compelling

- ✔ Well-tolerated
- ✔ Early trends of improvement in objective measures of disease activity
  - ✔ Fecal calprotectin
  - ✔ CRP
  - ✔ Central read histology
- ✔ Potential rapid onset of action
  - ✔ Objective measured after only 14 days of treatment

APPLIED | MOLECULAR | TRANSPORT

# Oral AMT-101 Trial Design

Bittoo Kanwar, MD  
Chief Medical Officer

# Enrolling Comprehensive Phase 2 Plan for Oral AMT-101

 market-uc combo

## UC Combination with anti-TNF $\alpha$

- Local disease
- Moderate-to-severe UC patients
- ~30 patients: biologic naïve
- 8-week oral daily dosing

 fillmore-pouchitis

## Pouchitis

- Local disease
- Chronic pouchitis patients
- ~20 patients: biologic naïve and experienced
- 12-week oral daily dosing

 lombard-uc

## UC Monotherapy

- Local disease
- Moderate-to-severe UC patients
- ~100 patients: biologic naïve and experienced
- 12-week oral daily dosing

 castro-ra combo

## RA Combination with anti-TNF $\alpha$

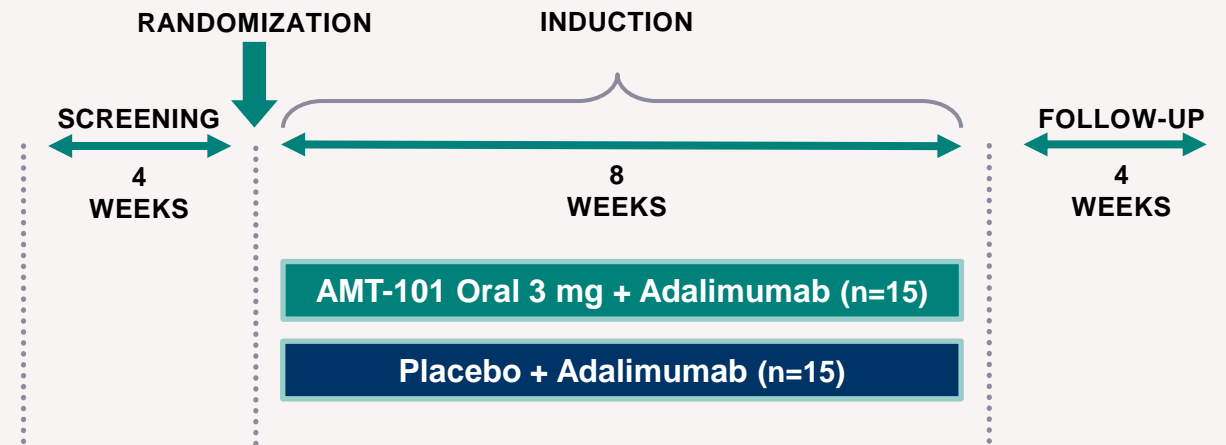
- Distal disease
- Patients with active RA who had an inadequate response to anti-TNF $\alpha$  therapy
- ~20 patients: biologic experienced
- 12-week oral daily dosing



# AMT-101: Phase 2 MARKET Study Design: UC Combination (8-week Induction Trial)

- Patient Population: Biologic naïve with moderate to severe UC
- AMT-101 Oral 3mg
- Baseline Mayo score of 6-12 with central read endoscopy of 2/3
- **Key efficacy endpoint: Mean change in UC-100**

## market-uc combo



- Key Secondary/Exploratory Endpoints:
  - Clinical Remission (Endoscopic subscore of 0/1, rectal bleeding 0, stool frequency 0/1)
  - Endoscopic response and remission
  - Histologic remission
  - Safety, PK, PD

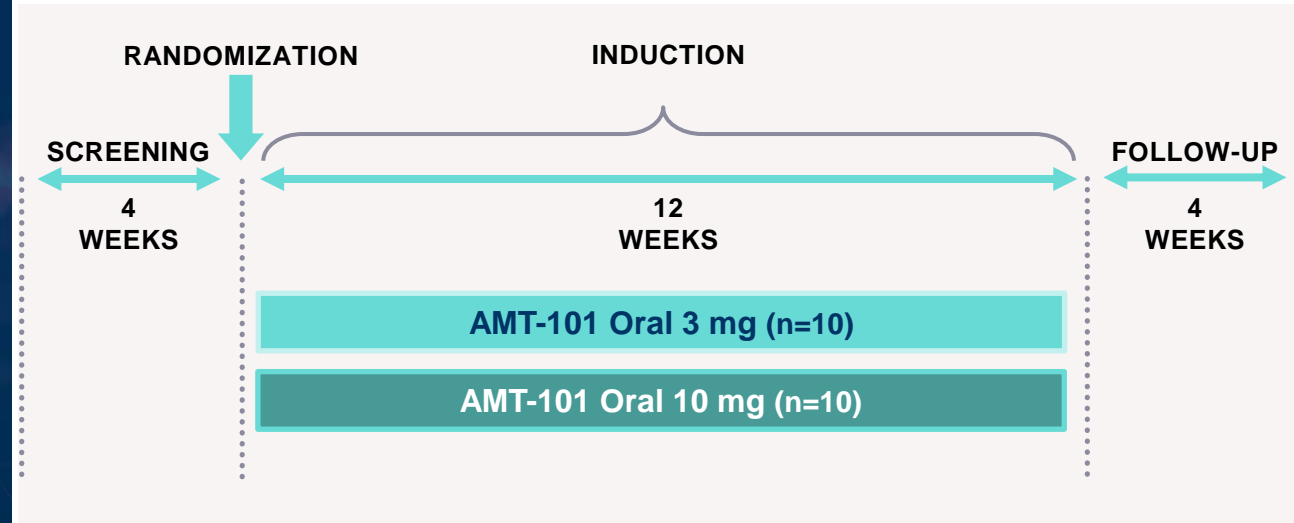
# AMT-101: Phase 2 FILLMORE Study Design: Chronic Pouchitis (12-week Induction Trial)

- Patient Population: UC patients s/p colectomy with chronic inflammation of the pouch
- Patients must have failed AT LEAST one round of antibiotic therapy
- Inclusion criteria based upon central read histology and stool frequency
- **Co-Primary endpoint:**
  - **Reduction of stool frequency of  $\geq 3$  AND 30% reduction from baseline or to post-colectomy normal**
  - **Histologic Healing (Geboes  $<3.1$ )**

APPLIED | MOLECULAR | TRANSPORT



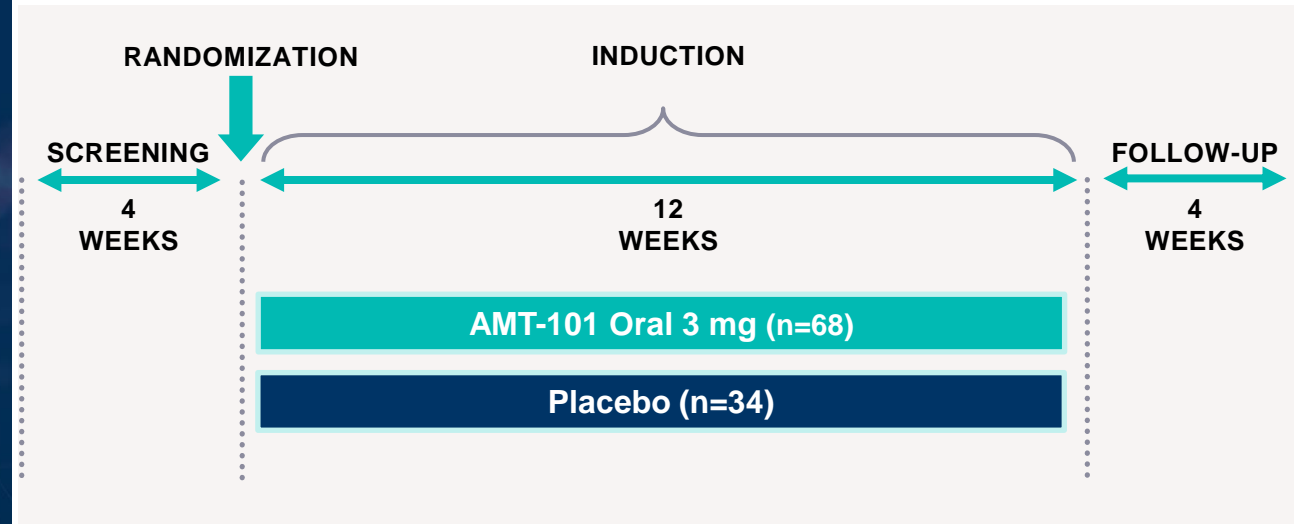
fillmore-pouchitis



- Key Secondary/Exploratory Endpoints:
  - Histologic response
  - Endoscopic response
  - Safety, PK, and PD

# AMT-101: Phase 2 LOMBARD Study Design: UC Monotherapy (12-week Induction Trial)

- Patient Population: Biologic naïve and experienced with moderate to severe UC
- Baseline Mayo score of 6-12 with central read endoscopy of 2/3
- **Primary endpoint: Mean change in endoscopic subscore**
- **Key efficacy endpoint: Clinical remission**



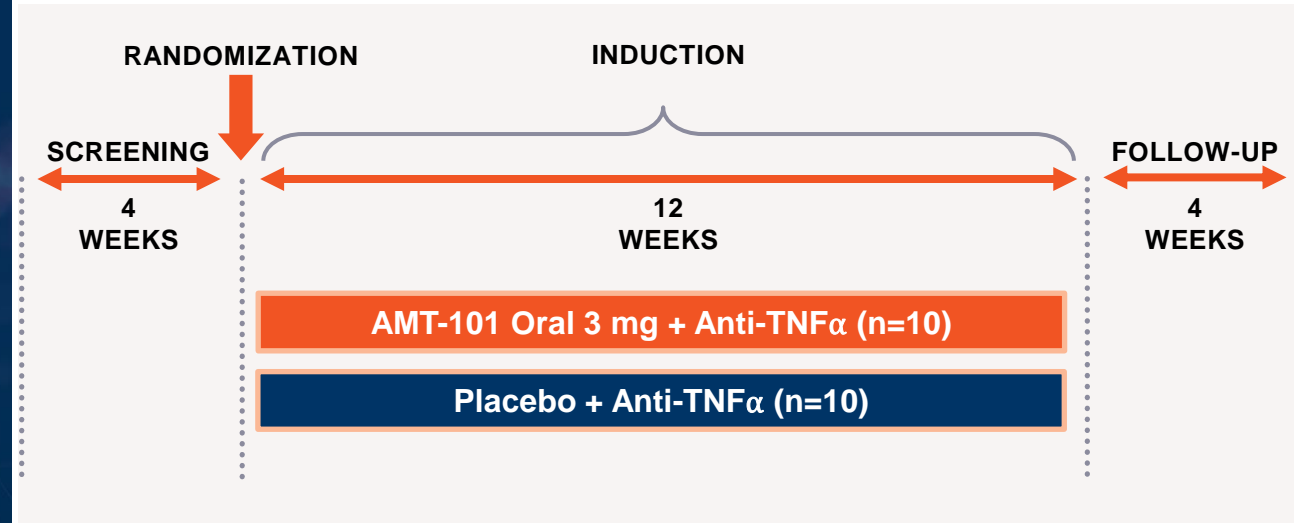
- Key Secondary/Exploratory Endpoints:
  - Clinical Remission (Endoscopic subscore of 0/1, rectal bleeding 0, stool frequency 0/1)
  - Endoscopic response and remission
  - Histologic remission
  - Safety, PK, PD

# AMT-101: Phase 2 CASTRO Study Design: RA Combination (12-week Induction Trial)

- Patient Population: Active RA with an inadequate response to anti-TNF therapy for  $\geq 16$  weeks
- Key inclusion criteria based upon DAS28 disease activity
- Must have minimum of 2 swollen joints for objective analysis of disease activity/response
- **Primary endpoint: Safety**
- **Key efficacy endpoint: DAS28CRP and ACR 20, 50, 70**







castro-ra



- Key Secondary/Exploratory Endpoints:
  - DAS28(CRP)
  - ACR 20, 50, 70
  - Ultrasound evaluation of swollen joint
  - PK, PD



# Summary of Anticipated AMT-101 Phase 2 Endpoints and Top-line Readouts

AMT-101 Phase 2 Trial	Summary Description	Key Efficacy Endpoints at Top-line Readout	Anticipated Top-line Data
 market-uc combo	UC combination with anti-TNF $\alpha$ +3mg AMT-101 or PBO	Clinical remission	Jan 2022
 fillmore-pouchitis	Pouchitis monotherapy 3mg or 10mg AMT-101	Reduction in stool frequency	H1 2022
 lombard-uc	UC monotherapy 3mg AMT-101 vs PBO	Clinical remission	H1 2022
 castro-ra combo	RA combination with anti-TNF $\alpha$ +3mg AMT-101 or PBO	DAS28/CRP ACR20/50/70	H2 2022

APPLIED | MOLECULAR | TRANSPORT

# Oral AMT-101 Commercial Opportunity

Liz Bhatt

Chief Business and Strategy Officer

# IBD: A Large and Growing Market Opportunity

## There are approximately 1.5M people living with IBD in the US

- ~300,000 IBD patients are treated with targeted therapies
- Growing market across all geographies

## Targeted therapy use is growing but adoption is still <50% in moderate to severe patients

- Lack of safe, effective, and convenient oral options

## A large majority of IBD patients not in remission at 1 year with today's treatment options

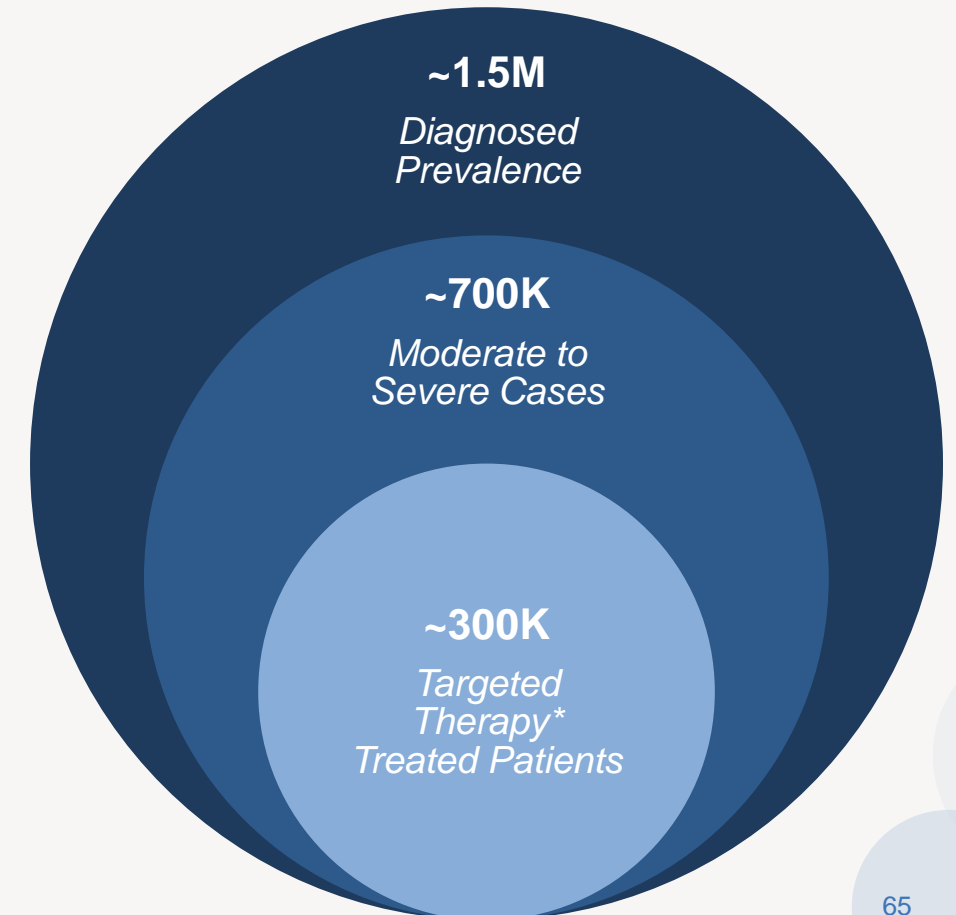
- Low response rates and/or loss of response
- Safety concerns, including black box warnings

Source: AMT Primary Market Research, 2021; Dahlhamer JM, et al. MMWR Morb Mortal Wkly Rep 2016;65:1166–1169; Schreiber, S. et al. J. Crohn's and Colitis 2013;7, 497-509; GlobalData, Ulcerative Colitis: Global Drug Forecast and Market Analysis to 2029, 2020; GlobalData, Crohn's Disease: Global Drug Forecast and Market Analysis to 2029, 2020.

APPLIED | MOLECULAR | TRANSPORT

\*Targeted Therapy defined as the group of treatments that include both targeted biologics (e.g., aTNFs) and targeted oral treatments (e.g., JAKi).

## UC & CD Market Potential (US, 2020)



# Significant Unmet Need Across UC Treatment Landscape

 **Significant  
Remaining  
Unmet Need**



Safe targeted therapies,  
no immunosuppression



Higher response and  
long-term durable remission



Oral dosing



Rapid onset of activity

*“We need to have drugs that have high efficacy and safety, and drugs that don’t increase the rate of serious infection and malignancy as much.” – IBD KOL*

*“Wish list for UC...tofacitinib efficacy + vedolizumab safety + oral + early onset of activity + fixed duration of treatment + prespecified patient population/responders” – IBD KOL*



# Compelling Product Profile for AMT-101 to Address Significant Unmet Needs

## AMT-101 IS AN ORAL BIOLOGIC ENGINEERED TO DELIVER BEST-IN-DISEASE SAFETY AND EFFICACY IN A CONVENIENT ONCE-DAILY TABLET



### EFFICACY

- Immunomodulator that restores immune homeostasis and promotes mucosal healing
- Rapid onset of action



### SAFETY

- Low systemic exposure resulting in favorable safety and tolerability profile



### DOSING

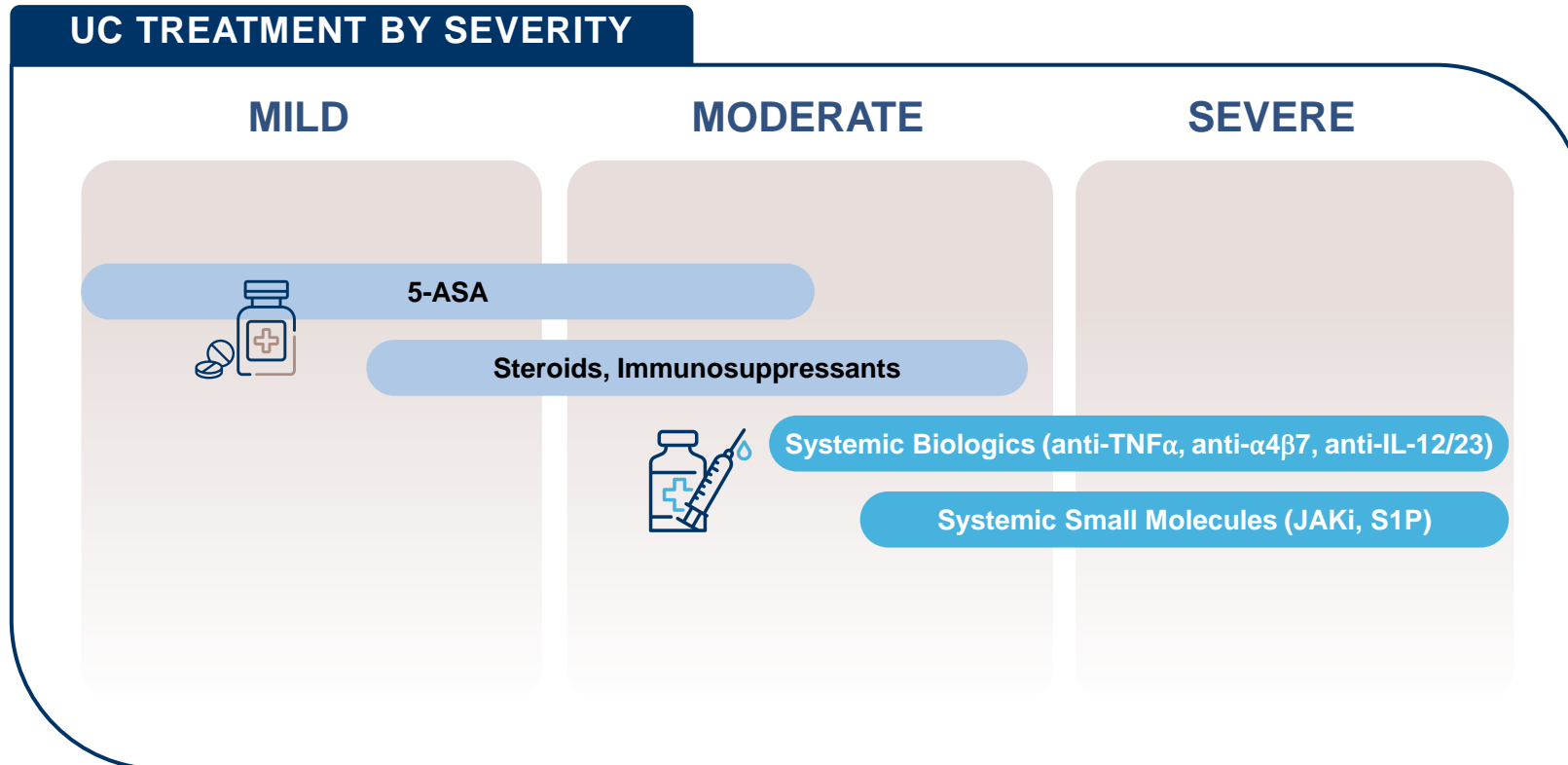
- Convenient, once-daily oral tablet



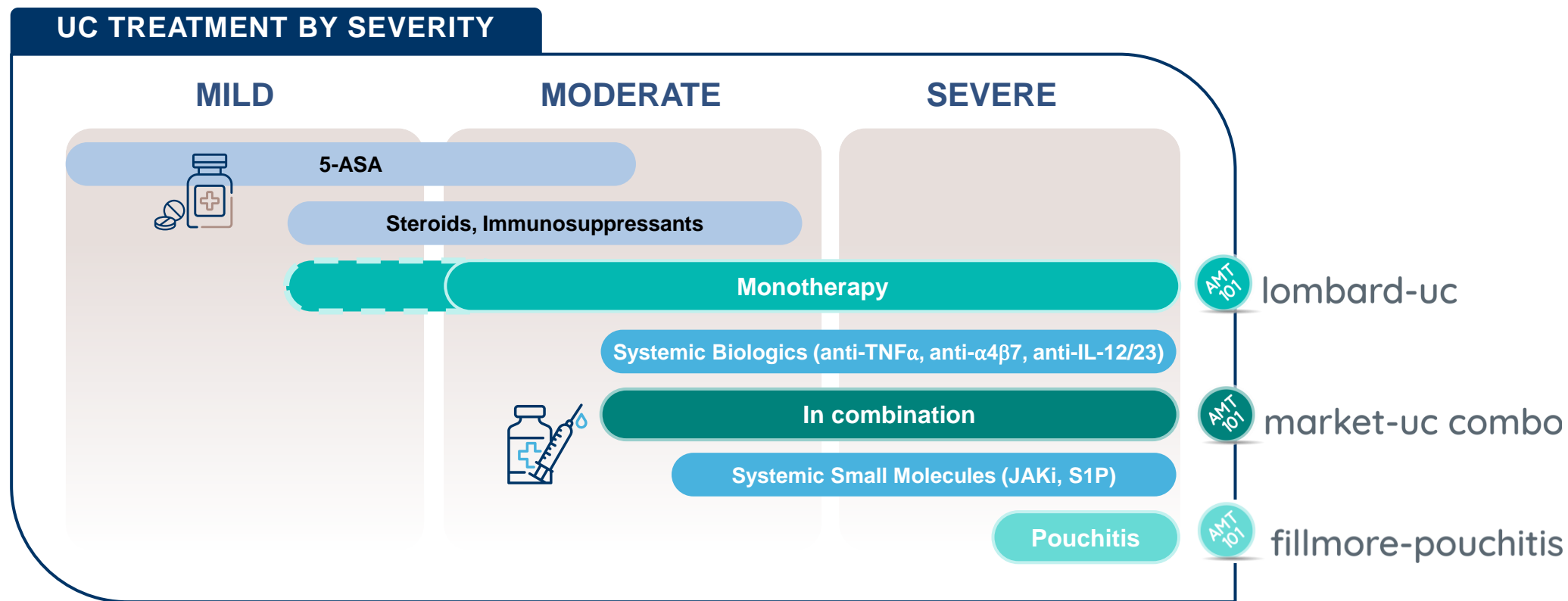
### PATIENTS

- Mono- and combination therapy options support early use across patient subgroups

# Opportunities Remain for New Therapies Across UC Disease Severity

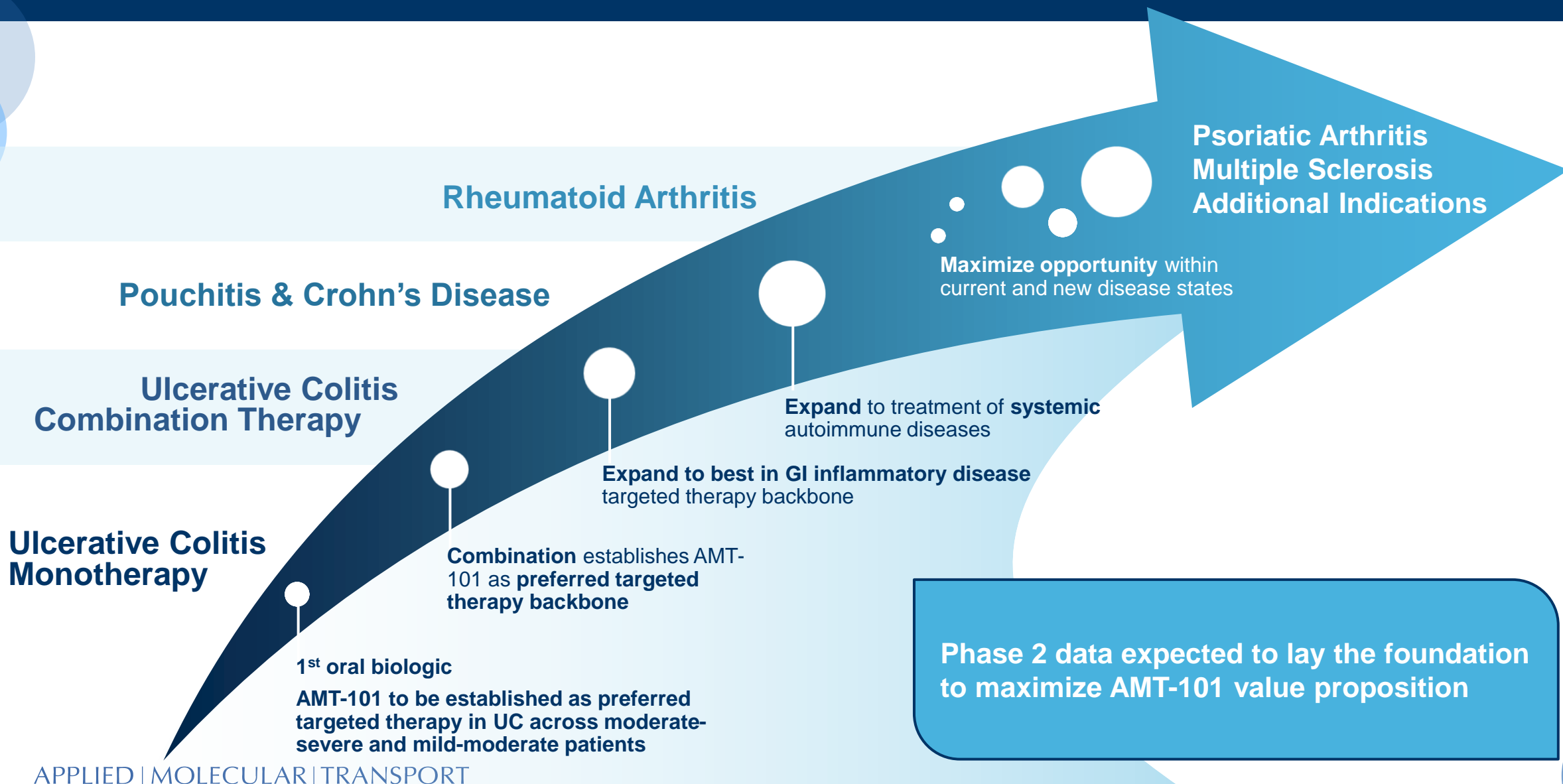


# Potential for AMT-101 Across UC Patient Populations



AMT-101 has the potential to redefine patient & physician experiences of biologic treatments

# AMT-101: Potential to Unlock a New Era of Patient Experiences Across Autoimmune and Inflammatory Diseases





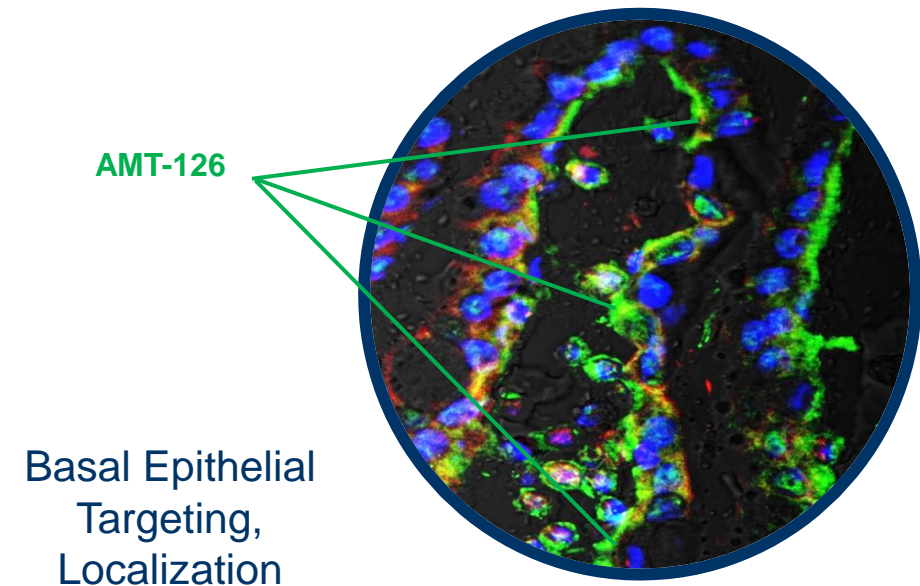
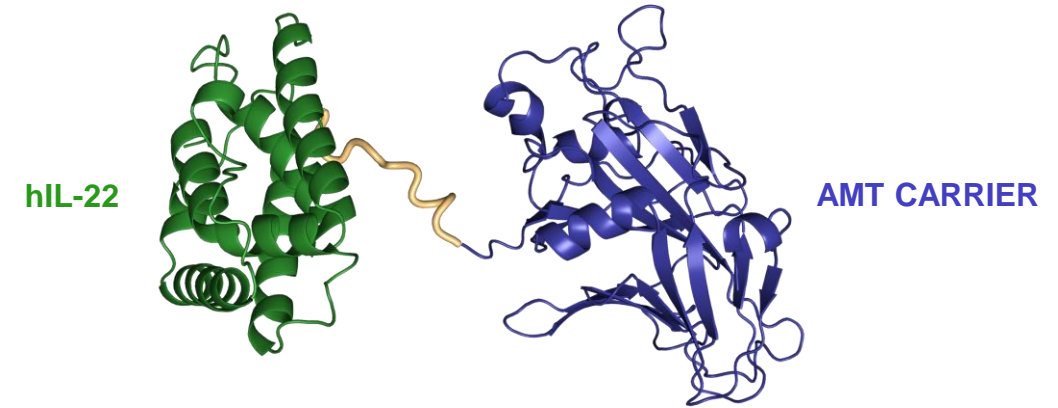
## The Future / Conclusion

Tahir Mahmood, PhD  
Chief Executive Officer and Co-Founder

# AMT-126: Phase 1 Trial Ongoing

- Oral, GI-selective daily biologic targeting repair and maintenance of epithelial barrier
- Clinically-validated mechanism of action
- Unique product profile with potential as single agent or in combination
- Program update in H1 2022

## Oral IL-22 Fusion Biologic



# IL-22 is a Clinically Validated Target

## UTTR1147A (Genentech/Roche)

- Systemic delivery of IL-22Fc showed therapeutic activity in a 12-week Ph 1b in UC patients<sup>1</sup>

	UTTR1147A	PLACEBO
Clinical Response	7/18 (39%)	1/6 (17%)
Clinical Remission	5/18 (28%)	0/6 (0%)

- Induced increases in serum PD biomarkers REG3A and C-reactive protein (CRP)
- Most common AEs were mechanism-related: dry skin, erythema, dry lip, skin discomfort, skin exfoliation, pruritis (1 subject withdrew due to treatment AE)

**JEM** Journal of Experimental Medicine

REVIEW  
Cytokines Focus

### The role of IL-22 in intestinal health and disease

Mary E. Keir<sup>1\*</sup>, Tangsheng Ye<sup>2\*</sup>, Timothy T. Lu<sup>3</sup>, and Nico Ghilardi<sup>4</sup>

The cytokine interleukin-22 (IL-22) is a critical regulator of epithelial homeostasis. It has been implicated in multiple aspects of epithelial barrier function, including antimicrobial defense, and disease (IBD).

**cmgh** CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

### ORIGINAL RESEARCH

#### Interleukin 22 Expands Transit-Amplifying Cells While Depleting Lgr5<sup>+</sup> Stem Cells via Inhibition of Wnt and Notch Signaling

Juan-Min Zha,<sup>1,2,a</sup> Hua-Shan Li,<sup>1,a</sup> Qian Lin,<sup>1,a</sup> Wei-Ting Kuo,<sup>3</sup> Zhi-Hui Jiang,<sup>1</sup> Pei-Yun Tsai,<sup>2</sup> Ning Ding,<sup>1</sup> Jia Wu,<sup>1</sup> Shao-Fang Xu,<sup>1</sup> Yi-Tang Wang,<sup>2</sup> Jian Pan,<sup>4</sup> Xiu-Min Zhou,<sup>1</sup> Kai Chen,<sup>1</sup> Jerrold R. Turner,<sup>2,3,b</sup>

#### A Randomized, Observer-Blinded, Phase Ib, Multiple Ascending-Dose Study of UTTR1147A, an IL-22Fc Fusion Protein, in Healthy Volunteers and Ulcerative Colitis Patients

Frank Wagner<sup>1</sup>, John Mansfield<sup>2</sup>, Christian Geier<sup>1</sup>, Ajit Dash<sup>2</sup>, Yehong Wang<sup>3</sup>, Chloe Li<sup>3</sup>, Annemarie Lekkerkerker<sup>3</sup>, Tim Lu<sup>3</sup>

<sup>1</sup>Charité Research Organization, Berlin, Germany; <sup>2</sup>The Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, United Kingdom; <sup>3</sup>Genentech, Inc., South San Francisco, CA, USA

**BACKGROUND**

- Inflammatory bowel disease (IBD) is characterized by gut dysbiosis, a weakened epithelial barrier, and a dysregulated immune system.
- Interleukin-22 (IL-22), an IL-10 family cytokine, has demonstrated efficacy in animal IBD models by promoting intestinal epithelial repair, increasing antimicrobial peptide production, and increasing mucin production via goblet cells.
- UTTR1147A is a fusion protein in which IL-22 is linked with the Fc portion of immunoglobulin (Ig)G4 to improve pharmacokinetic (PK) characteristics.
- UTTR1147A activated the IL-22 pathway in preclinical studies and a Phase Ia trial<sup>2</sup> as shown by elevations in:
  - C-reactive protein (CRP), an acute phase liver protein produced during hepatocyte stimulation<sup>3</sup>
  - Regenerating islet protein 3A (REG3A), a C-type lectin primarily in Paneth cells, and in IBD, in metastatic small intestine, and stomach<sup>4</sup>

**METHODS**

**Objective**

- A phase I study (NCT02749630) was conducted to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of UTTR1147A in healthy volunteers (HVs) and patients with ulcerative colitis (UC).

**Study Design**

- Randomized, observer-blinded, phase Ib, multiple ascending dose.

**Pharmacokinetics**

**Figure 2. UTTR1147A Pharmacokinetics in HVs and UC Patients.**

**Figure 2A. HV**

**Figure 2B. UC**

Received: 25 August 2018 | Revised: 6 September 2018 | Accepted: 7 September 2018  
DOI: 10.1002/ppp2.434

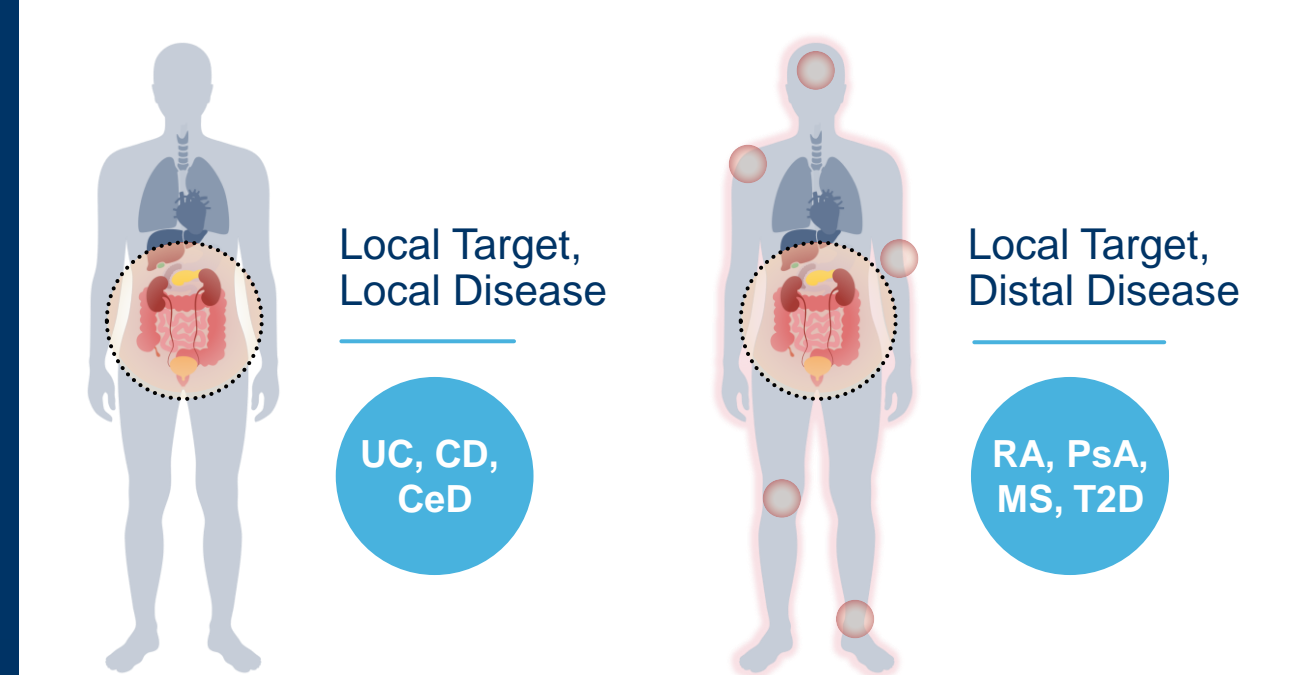
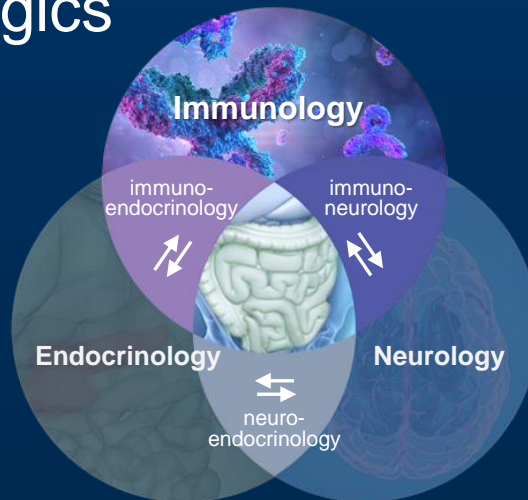
**ORIGINAL ARTICLE**

### Nonclinical safety assessment of a human interleukin-22Fc IG fusion protein demonstrates in vitro to in vivo and cross-species translatability

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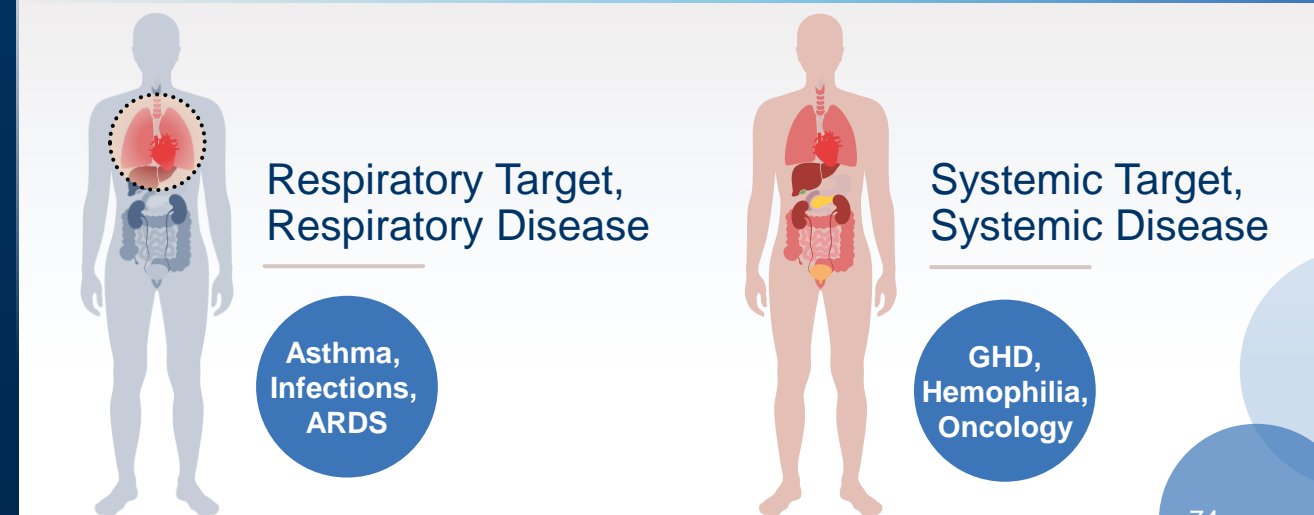
# GOAL OF TARGETED THERAPEUTICS IS TO PROVIDE SIGNIFICANT BENEFITS

- Improved efficacy
- Better safety profile
- Ability to access pathways in a unique way
- Selectivity of biologics



## CURRENT CLINICAL FOCUS

## RESEARCH PIPELINE





# SUMMARY



**Clinical Stage**, Transformational Targeted **Oral Biologics** –  
**Validated Targets** for Significant Unmet Medical Needs



Rich **Data Catalyst** Readout Calendar



Goal of Enhanced **Efficacy & Safety**



**End-to-End**, Scalable R&D and Manufacturing  
Capabilities

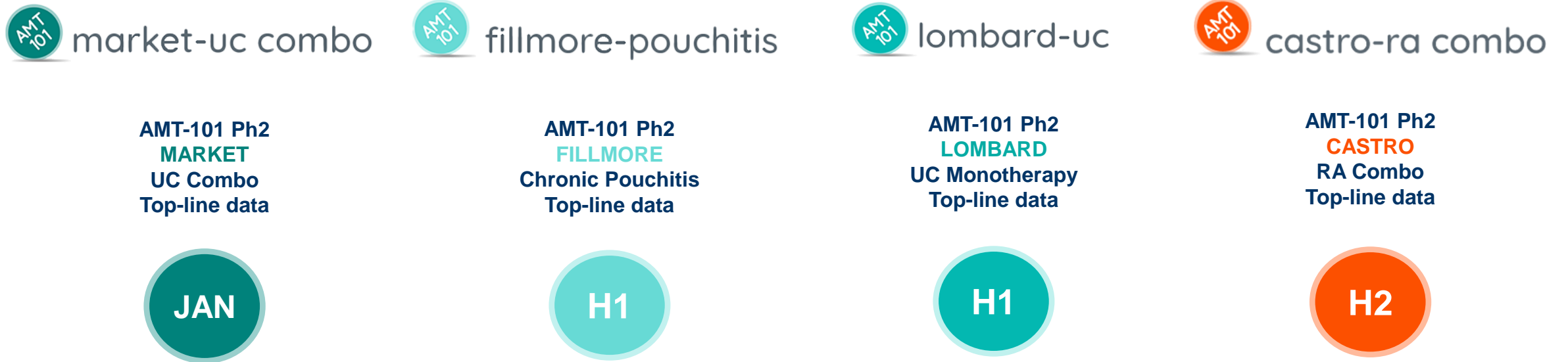


Accomplished, **World-class** Leaders and Team



**Well-Capitalized**

# Anticipated Oral AMT-101 Milestones in 2022



APPLIED | MOLECULAR | TRANSPORT

**Thank you and Q&A**

# Breakthrough Medicines. The Next Age of Biologics.

