PRAXIS
PEPTIDE INSTITUTE

GLP-2

ADVANCED MECHANISM AND EVIDENCE GUIDE

ENDOGENOUS INTESTINOTROPHIC AND PRO-ABSORPTIVE PEPTIDE
33 amino acids • L cells • GLP-2R • mucosa • barrier • blood flow • absorption • teduglutide

MEMORY KEY: GLP-2 HELPS THE REMAINING INTESTINE BUILD MORE FUNCTIONAL CAPACITY.

Educational monograph • Established intestinal physiology • Strong human validation in short bowel syndrome with intestinal failure

HOW TO USE THIS GUIDE

This guide converts a long-form research narrative into a repeatable learning system. Every future PPI molecule guide can use the same architecture, visual language, evidence labels, and memory devices.

01	IDENTITY What it is - and what it is not
02	PHYSIOLOGY The normal system before the compound
03	MECHANISM Target, pathway, and downstream logic
04	EVIDENCE Cell, animal, and human evidence separated
05	RISK Known concerns, unknowns, and translation limits
06	MONITORING What a legitimate research framework would measure
07	PATIENT CONTEXT Which phenotype might fit the biology
08	RECALL Memory hooks, seven questions, and bottom line

EVIDENCE CODE		CORE DISCIPLINE
	CELL = mechanistic ANIMAL = organism-level preclinical HUMAN = clinical translation	Mechanism does not equal outcome. Unknown does not equal failed - and unknown does not equal proven.

RAPID RECALL

Read this page first. These anchors provide the complete high-level story of Glp-2; the remaining pages add mechanism, evidence, context, and nuance.

01	IDENTITY A 33-amino-acid proglucagon-derived hormone released mainly by intestinal L cells after nutrient exposure.
02	RECEPTOR GLP-2R signaling is largely indirect, coordinating enteric neurons, stromal cells, IGF pathways, KGF, and local mediators.
03	STRUCTURE Supports crypt proliferation, epithelial survival, villus height, mucosal mass, and absorptive surface area.
04	FUNCTION Coordinates barrier integrity, mesenteric blood flow, gastric transit, secretion, nutrient uptake, and fluid absorption.
05	TIME Native GLP-2 is rapidly cleaved by DPP-4; teduglutide extends receptor exposure through analog engineering.
06	CLINICAL PROOF In short bowel syndrome with intestinal failure, improved absorption can reduce parenteral fluid and nutrition needs.
07	RISK LOGIC Greater absorption and growth require monitoring for fluid overload, altered drug exposure, and pre-existing abnormal tissue.
08	PRAXIS QUESTION Is lost intestinal capacity the bottleneck, and did objective absorption or independence improve?

ONE-SENTENCE MEMORY
GLP-2 HELPS THE REMAINING INTESTINE BUILD MORE FUNCTIONAL CAPACITY.

UNDERSTAND THE PEPTIDE

GLP-2 - glucagon-like peptide-2 - is a 33-amino-acid peptide hormone derived from proglucagon and secreted predominantly by enteroendocrine L cells in the distal small intestine and colon after nutrient exposure.

Its dominant biological role is not:

GLUCOSE CONTROL.

That belongs much more strongly to:

GLP-1.

GLP-2 has a very different job.

Its biology is centered on:

- intestinal growth
- barrier function
- fluid absorption
- gastric emptying
- intestinal adaptation after bowel loss
- mucosal integrity
- nutrient absorption
- mesenteric blood flow
- gastric secretion

This makes GLP-2 one of the clearest examples of:

A PEPTIDE THAT HELPS THE GUT ADAPT TO WHAT HAS BEEN LOST OR DAMAGED.

A major physiological review describes GLP-2 as an intestinal hormone that increases intestinal growth, digestion, absorption, barrier function, and blood flow, with these effects translating into meaningful human benefit in intestinal failure.

The best way to understand GLP-2 is not:

“A GUT-HEALING PEPTIDE.”

That is too vague.

A better description is:

AN INTESTINOTROPHIC AND PRO-ABSORPTIVE PEPTIDE HORMONE THAT COORDINATES MUCOSAL GROWTH, BARRIER INTEGRITY, BLOOD FLOW, MOTILITY, AND NUTRIENT HANDLING TO INCREASE THE FUNCTIONAL CAPACITY OF THE INTESTINE.

That is the core biology.

WHAT IS GLP-2?

GLP-2 is a:

33-AMINO-ACID PEPTIDE.

It is produced from the:

PROGLUCAGON PRECURSOR.

That same precursor can generate different peptides depending on:

WHERE IT IS PROCESSED.

This is important.

In pancreatic alpha cells, proglucagon processing favors:

GLUCAGON.

In intestinal L cells and selected neurons, different convertase activity generates:

GLP-1

GLP-2

- oxyntomodulin
- glicentin-related peptides

So:

ONE PRECURSOR

can create:

MULTIPLE HORMONES WITH VERY DIFFERENT JOBS.

That is a beautiful example of:

TISSUE-SPECIFIC PEPTIDE PROCESSING.

THE IDENTITY MODEL

PROGLUCAGON	→	**Intestinal L-cell processing**	→	**GLP-1**
GLP-2		→		**After nutrient ingestion:**
GLP-2 RELEASE	→	**GLP-2 RECEPTOR**	→	**Potential:**

INTESTINAL GROWTH

BARRIER SUPPORT

BLOOD FLOW ↑

GASTRIC EMPTYING ↓

GASTRIC SECRETION ↓

ABSORPTION ↑	→	**Potential:**

BETTER INTESTINAL ADAPTATION

The central idea is:

GLP-2 HELPS THE GUT BECOME MORE FUNCTIONALLY CAPABLE.

WHERE IS GLP-2 PRODUCED?

GLP-2 is secreted primarily by:

ENTEROENDOCRINE L CELLS.

These are especially abundant in the:

• distal ileum

• colon

Nutrients entering the gut stimulate release.

Important triggers include:

• carbohydrates

• fats

• mixed meals

Interestingly, nutrients do not always need to physically reach every distal L cell before GLP-2 rises.

Neural and endocrine signaling can contribute to:

EARLY RELEASE.

This reinforces that the intestine is not simply:

A PIPE ABSORBING NUTRIENTS.

It is:

AN ENDOCRINE ORGAN.

GLP-1 AND GLP-2 - SAME CELL, DIFFERENT JOBS

GLP-1 and GLP-2 are commonly:

CO-SECRETED.

But their dominant biological identities differ significantly.

GLP-1

Primary themes:

- insulin secretion
- appetite
- glucose control
- glucagon regulation
- gastric emptying

GLP-2

Primary themes:

- intestinal growth
- barrier integrity
- intestinal adaptation
- absorption
- intestinal blood flow

So:

GLP-1 HELPS REGULATE WHAT HAPPENS AFTER NUTRIENTS ENTER THE BODY.

GLP-2 helps regulate:

THE INTESTINAL SYSTEM THAT ALLOWS THOSE NUTRIENTS TO ENTER THE BODY IN THE FIRST PLACE.

That distinction is fundamental.

THE GLP-2 RECEPTOR

GLP-2 signals through:

GLP-2R - GLUCAGON-LIKE PEPTIDE-2 RECEPTOR.

GLP-2R is a:

G-PROTEIN-COUPLED RECEPTOR.

Its signaling can involve:

- cAMP
- PKA-related pathways
- MAPK-related signaling

But there is an important twist.

The receptor is not concentrated primarily on:

THE CRYPT CELLS THAT ACTUALLY PROLIFERATE.

Instead, GLP-2R is expressed on selected cells including:

- enteric neurons
- enteroendocrine cells
- subepithelial myofibroblast-related populations

That means many GLP-2 effects are:

INDIRECT.

This is one of the most interesting aspects of GLP-2 biology.

THE INDIRECT-SIGNALING MODEL

GLP-2	→	**GLP-2R on selected intestinal regulatory cells**	→	**Secondary mediators released**

Examples:

IGF-1

IGF-2

ERBB LIGANDS

KERATINOCYTE GROWTH FACTOR

VIP

NITRIC OXIDE	→	**Effects on:**

CRYPT PROLIFERATION

MUCOSAL GROWTH

BLOOD FLOW

BARRIER FUNCTION	→	**Potential:**

INTESTINAL ADAPTATION

This means GLP-2 is less like:

A DIRECT EPITHELIAL GROWTH SWITCH

and more like:

A COORDINATOR OF THE REPAIR ENVIRONMENT.

INTESTINOTROPHIC BIOLOGY

GLP-2 is commonly described as:

INTESTINOTROPHIC.

That means it promotes:

GROWTH AND MAINTENANCE OF INTESTINAL TISSUE.

Experimental and human research has demonstrated increases in:

- villus height
- crypt depth
- mucosal mass

with sustained GLP-2 receptor activation.

That has major functional implications.

A larger healthy absorptive surface can potentially:

ABSORB MORE FLUID + NUTRIENTS.

VILLUS BIOLOGY

The small intestine contains:

VILLI.

These finger-like structures massively increase:

ABSORPTIVE SURFACE AREA.

Imagine the difference between:

A FLAT WALL

and:

A WALL COVERED WITH THOUSANDS OF FOLDS.

Villi dramatically increase the amount of epithelial surface available for:

- carbohydrate absorption
- lipid handling
- micronutrient uptake
- amino-acid absorption
- fluid transport

GLP-2 can increase:

VILLUS HEIGHT.

That means:

MORE FUNCTIONAL ABSORPTIVE SURFACE.

THE VILLUS MODEL

GLP-2 → **Intestinal trophic signaling** → **Villus height ↑** → **Mucosal surface area ↑** → **Potential:**

NUTRIENT ABSORPTION ↑

FLUID ABSORPTION ↑

This is why GLP-2 is especially powerful when the patient has:

TOO LITTLE FUNCTIONAL BOWEL.

CRYPT BIOLOGY

The intestinal epithelium turns over rapidly.

New epithelial cells originate largely from:

CRYPT STEM / PROGENITOR CELLS.

They proliferate. → **Differentiate.** → **Migrate upward.** → **Replace older epithelial cells.**

GLP-2 enhances:

CRYPT CELL PROLIFERATION

and can reduce:

EPITHELIAL APOPTOSIS.

So the peptide simultaneously influences:

CELL PRODUCTION

and:

CELL SURVIVAL.

THE MUCOSAL-GROWTH MODEL

CRYPT PROLIFERATION ↑

APOPTOSIS ↓ → **More viable epithelial cells** → **Villus architecture improves** → **Mucosal mass ↑** → **Potential:**

ABSORPTIVE CAPACITY ↑

Again:

this is not simply:

“HEAL THE LINING.”

It is:

INCREASE THE STRUCTURAL CAPACITY OF THE LINING.

BARRIER FUNCTION

The intestine has two competing jobs.

It must allow:

NUTRIENTS IN

while keeping:

MICROBES + TOXINS + LUMINAL CONTENT

appropriately compartmentalized.

That is:

BARRIER FUNCTION.

GLP-2 has been shown to:

- improve epithelial integrity
- reduce intestinal permeability
- support mucosal defense

reduce injury in multiple preclinical gut-stress models.

This makes GLP-2 biologically relevant far beyond:

SHORT BOWEL LENGTH.

THE BARRIER MODEL

Healthy:

TIGHT JUNCTIONS + MUCUS + EPITHELIAL INTEGRITY

Selective absorption	→	**Microbes remain appropriately compartmentalized**		
Damaged barrier:	→	**Permeability ↑**	→	**Luminal antigens / microbial products cross more easily** → **Immune activation ↑**
GLP-2	→	**Potential:**		
BARRIER INTEGRITY ↑	→	**Potential:**		

ABNORMAL TRANSPORT ↓

Again:

barrier function is:

REGULATION.

Not simply:

“CLOSE THE GUT.”

GLP-2 AND MUCOSAL BLOOD FLOW

Digestion and absorption require:

BLOOD FLOW.

After a meal:

the intestine must transport absorbed nutrients away from the mucosa.

GLP-2 increases:

MESENTERIC BLOOD FLOW.

This effect appears to involve:

ENTERIC NEURAL SIGNALING

and:

NITRIC OXIDE.

Again:

better intestinal function requires more than:

MORE EPITHELIAL CELLS.

Those cells require:

- oxygen
- nutrients
- vascular transport

THE BLOOD-FLOW MODEL

GLP-2 → **Enteric neural signaling** → **Nitric oxide** → **Mesenteric vasodilation** → **INTESTINAL BLOOD FLOW ↑** → **Potential:**

NUTRIENT TRANSPORT + TISSUE SUPPORT ↑

This is why GLP-2 is really:

A COORDINATOR OF INTESTINAL FUNCTION.

GASTRIC EMPTYING

GLP-2 can:

SLOW GASTRIC EMPTYING.

Why might that be useful?

If food leaves the stomach too quickly:

the remaining intestine receives:

A LARGE NUTRIENT AND FLUID LOAD ALL AT ONCE.

In short bowel syndrome:

that can increase:

- diarrhea
- fluid losses
- malabsorption

Slower delivery may give the remaining intestine:

MORE TIME TO ABSORB.

GASTRIC SECRETION

GLP-2 can also reduce:

GASTRIC ACID / SECRETORY OUTPUT.

Again:

this may be highly relevant after massive bowel resection.

Less secretion into the GI lumen means:

LESS FLUID THAT LATER NEEDS TO BE REABSORBED.

This creates a beautiful physiological strategy:

INCREASE ABSORPTION

while also:

REDUCING SECRETORY LOSSES.

THE NET-FLUID MODEL

GLP-2 → **ABSORPTION ↑**

plus:

GASTRIC SECRETION ↓

plus:

GASTRIC EMPTYING SLOWS

Potential:

STOOL / OSTOMY OUTPUT ↓

Potential:

PARENTERAL FLUID NEED ↓

This is exactly what makes the pathway so useful in:

SHORT BOWEL SYNDROME.

DPP-4 DEGRADATION

Native GLP-2 is rapidly degraded by:

DPP-4 - DIPEPTIDYL PEPTIDASE-4.

DPP-4 cleaves:

GLP-2(1-33)

into:

GLP-2(3-33),

which has greatly reduced agonist activity.

This gives native GLP-2 a:

SHORT HALF-LIFE.

That became the central pharmacological problem.

How do you preserve the biology:

WITHOUT RAPID DPP-4 DESTRUCTION?

Enter:

TEDUGLUTIDE.

TEDUGLUTIDE

Teduglutide is a:

GLP-2 ANALOG.

Its sequence differs from native GLP-2 at position 2.

The alanine normally present there is replaced by:

GLYCINE.

That seemingly small change makes the peptide much more resistant to:

DPP-4 CLEAVAGE.

This dramatically increases biological exposure.

Again:

ONE AMINO-ACID CHANGE

can fundamentally alter:

PHARMACOKINETICS.

That is peptide engineering.

NATIVE GLP-2 VS TEDUGLUTIDE

NATIVE GLP-2

- endogenous
- rapidly degraded by DPP-4
- 33 amino acids
- short biological exposure

TEDUGLUTIDE

- GLP-2 analog
- longer-acting
- maintains GLP-2R agonism
- DPP-4 resistant
- clinically usable

Again:

ANALOG EVIDENCE ≠ EXACTLY THE SAME AS NATIVE-PEPTIDE EVIDENCE.

But in this case:

the analog was explicitly designed to preserve:

THE SAME RECEPTOR BIOLOGY LONGER.

SHORT BOWEL SYNDROME

This is where GLP-2 biology became:

CLINICAL MEDICINE.

Short bowel syndrome occurs when the intestine has insufficient functional length to adequately absorb:

• nutrients

• fluids

• electrolytes

after extensive bowel resection or severe loss of functional surface.

Some patients develop:

INTESTINAL FAILURE.

That means they require:

PARENTERAL SUPPORT

to survive.

This can include:

• intravenous fluids

• parenteral nutrition

The biological problem is straightforward:

TOO LITTLE ABSORPTIVE CAPACITY.

GLP-2 directly addresses:

THAT BOTTLENECK.

THE SHORT-BOWEL MODEL

Massive bowel loss	→	**Surface area ↓**	→	**Fluid absorption ↓**
Nutrient absorption ↓	→	**High output / malabsorption**	→	**Parenteral support required**
Teduglutide / GLP-2R activation	→	**VILLUS HEIGHT ↑**		

MUCOSAL MASS ↑

ABSORPTION ↑

SECRETORY LOSSES ↓	→	**Potential:**

PARENTERAL SUPPORT ↓

This is one of the cleanest examples in peptide medicine of:

PHYSIOLOGY → MECHANISM → CLINICAL OUTCOME.

THE STEPS TRIAL

A pivotal 24-week randomized trial included:

86 patients with short bowel syndrome-associated intestinal failure.

Patients received teduglutide:

• 0.05 mg/kg/day

or placebo.

The response definition required at least:

20% REDUCTION IN PARENTERAL SUPPORT

at weeks 20 and 24.

Results:

• 63%

• of teduglutide-treated patients responded

versus:

• 30%

with placebo.

Mean parenteral-volume reduction was approximately:

• 4.4 L/week

• with teduglutide

versus:

• 2.3 L/week

with placebo.

That is not merely:

A BIOMARKER CHANGE.

That is:

THE PATIENT NEEDING LESS INTRAVENOUS SUPPORT TO SURVIVE.

WHY THAT MATTERS

Parenteral nutrition is lifesaving.

But long-term parenteral support can bring:

- line infections
- liver complications
- substantial lifestyle burden
- thrombosis
- fluid-management challenges

So reducing parenteral dependence can have:

REAL FUNCTIONAL VALUE.

Again:

the meaningful outcome is not:

“VILLUS HEIGHT WENT UP.”

It is:

“THE PATIENT ABSORBED ENOUGH TO NEED LESS PARENTERAL SUPPORT.”

LONG-TERM RESPONSE

GLP-2 therapy also teaches an important lesson about:

TIME.

Some patients do not demonstrate their maximal benefit at:

24 WEEKS.

Long-term studies show some patients continue to reduce parenteral support over:

MONTHS TO YEARS.

In the STEPS-3 extension, patients treated long term continued to reduce parenteral support, and some achieved complete enteral autonomy.

Real-world data similarly suggest that response can continue to increase after the first year.

That tells us:

INTESTINAL ADAPTATION TAKES TIME.

STRUCTURAL CHANGE IS SLOWER THAN SYMPTOM CHANGE

This distinction is important.

A stimulant can change:

HOW SOMEONE FEELS

within hours.

But GLP-2 can change:

THE STRUCTURE OF THE INTESTINE.

That requires:

- cell proliferation
- villus growth
- tissue remodeling
- functional adaptation

Those processes occur over:

TIME.

Again:

THE TIMELINE SHOULD MATCH THE MECHANISM.

TEDUGLUTIDE IS ESTABLISHED CLINICAL PEPTIDE MEDICINE

Teduglutide is marketed as:

GATTEX.

The FDA initially approved it in 2012 for adults with short bowel syndrome dependent on parenteral support; the indication later expanded to pediatric patients age 1 year and older.

That matters for PPI.

GLP-2 is not merely:

AN INTERESTING EXPERIMENTAL PEPTIDE.

The pathway is:

CLINICALLY VALIDATED.

GLP-2 AND INTESTINAL ADAPTATION

After bowel resection, the intestine naturally attempts to:

ADAPT.

The remaining intestine can:

- increase villus height
- alter transport
- increase absorptive efficiency
- enlarge diameter
- slow transit

GLP-2 appears to participate in:

THAT NATURAL ADAPTIVE RESPONSE.

Teduglutide essentially asks:

CAN WE PHARMACOLOGICALLY AMPLIFY THE BODY'S OWN ADAPTATION PROGRAM?

That is a central peptide-medicine concept.

THE ADAPTATION MODEL

Bowel resection → **Nutrients contact remaining intestine** → **L-cell signaling** → **GLP-2 ↑** → **Mucosal adaptation**

Teduglutide → **Amplifies GLP-2R signaling** → **Potential:**

GREATER STRUCTURAL + FUNCTIONAL ADAPTATION

This is not:

REPLACING THE MISSING BOWEL.

It is:

HELPING THE REMAINING BOWEL DO MORE WORK.

BARRIER INJURY AND MUCOSITIS

GLP-2 has also shown compelling preclinical effects in:

- chemotherapy-associated mucositis
- ischemic gut injury
- enteritis
- inflammatory bowel injury
- experimentally induced colitis

because its biology includes:

- epithelial proliferation
- reduced apoptosis
- barrier support

mucosal repair.

This creates obvious translational interest.

But:

THE EVIDENCE MATURITY IS VERY DIFFERENT FROM SBS.

That distinction must remain clear.

GLP-2 AND INFLAMMATORY BOWEL DISEASE

GLP-2 may theoretically help in IBD by:

- supporting epithelial repair
- improving mucosal integrity
- reducing permeability
- modulating inflammatory signaling indirectly

But IBD is fundamentally:

AN IMMUNE-MEDIATED DISEASE.

So repairing the epithelium does not necessarily:

CONTROL THE PRIMARY IMMUNE DRIVER.

Again:

BARRIER REPAIR ≠ IMMUNE REMISSION.

This is an important PPI distinction.

GLP-2 AND “LEAKY GUT”

Because GLP-2 improves barrier biology, it is often pulled into discussions of:

“LEAKY GUT.”

That can become biologically sloppy.

Increased intestinal permeability can occur in:

- celiac disease

IBD

- infection
- NSAID exposure
- severe illness
- metabolic disease

But:

“LEAKY GUT” IS NOT ONE DIAGNOSIS.

So the better question is:

WHY IS THE BARRIER DAMAGED?

GLP-2 may potentially support:

THE REPAIR SIDE OF THE EQUATION.

But the driver still matters.

GLP-2 AND VIP

These peptides overlap in:

BARRIER AND INTESTINAL BIOLOGY.

But their dominant identities differ.

VIP

Primary themes:

- neuroimmune signaling
- vascular tone
- immune modulation
- smooth-muscle regulation
- secretion

GLP-2

Primary themes:

- mucosal growth
- barrier integrity
- absorption
- intestinal adaptation

Interestingly, some GLP-2 anti-inflammatory and mucosal effects appear to be mediated indirectly through:

VIP RELEASE FROM ENTERIC NEURONS.

This is a beautiful example of:

PEPTIDES TALKING TO OTHER PEPTIDE SYSTEMS.

GLP-2 AND IGF SIGNALING

GLP-2-induced intestinal growth is not entirely direct.

Several studies implicate:

IGF-1

IGF-2

• IGF-1 receptor signaling

in crypt and mucosal proliferation.

This creates a model:

GLP-2

GLP-2R → **Local mediator** → **IGF SIGNALING** → **Crypt proliferation**

Again:

PRIMARY RECEPTOR LOCATION

and:

FINAL BIOLOGICAL EFFECT LOCATION

can be different.

That is an important systems-biology lesson.

GLP-2 AND KERATINOCYTE GROWTH FACTOR

In colonic tissue, GLP-2-related growth has also been linked to:

KERATINOCYTE GROWTH FACTOR - KGF.

Again:

GLP-2 does not simply tell every epithelial cell:

“GROW.”

It coordinates:

A NETWORK OF LOCAL MEDIATORS.

That makes GLP-2 more like:

A MASTER ADAPTATION SIGNAL

than:

A SINGLE CELL-TYPE GROWTH FACTOR.

INTESTINAL BLOOD FLOW AND NITRIC OXIDE

The blood-flow effects appear linked to:

NITRIC OXIDE.

Again:

GLP-2R activation on neural / regulatory cells can lead to:

VASCULAR RESPONSE.

This illustrates that improved absorption requires:

EPITHELIUM + VASCULATURE + ENTERIC NERVES.

A healthy intestine is:

A MULTISYSTEM ORGAN.

NEOPLASIA - THE CORRECT CONTEXT

Because GLP-2 promotes:

MUCOSAL GROWTH,

a rational biological question is:

WHAT HAPPENS IF ABNORMAL CELLS ARE ALREADY PRESENT?

A systematic review found no demonstrated increase in intestinal neoplasia with limited-duration human GLP-2 exposure in patients without known pre-existing cancer, but animal work suggested GLP-2 can accelerate growth of already initiated neoplastic lesions.

This is why the appropriate interpretation is not:

“GLP-2 CAUSES CANCER.”

That is not supported.

The more precise statement is:

A GROWTH-PROMOTING INTESTINAL SIGNAL MAY HAVE DIFFERENT CONSEQUENCES IN NORMAL MUCOSA VERSUS PRE-EXISTING ABNORMAL TISSUE.

That is mechanism-based reasoning.

WHY COLONOSCOPY MATTERS WITH TEDUGLUTIDE

The current U.S. prescribing information recommends intestinal-polyp surveillance before and during teduglutide treatment because of its intestinotrophic activity.

Again:

this is not because the peptide has been proven to:

CREATE CANCER FROM NORMAL TISSUE.

It reflects the more biologically grounded concern that:

GROWTH SIGNALS CAN ACCELERATE PRE-EXISTING ABNORMAL GROWTH.

That is the appropriate context.

FLUID BALANCE

One practical consequence of successful GLP-2 therapy is that:

ABSORPTION CAN IMPROVE SUBSTANTIALLY.

That sounds entirely beneficial.

But if parenteral fluids are not adjusted:

the patient can potentially develop:

FLUID OVERLOAD.

Again:

a therapy working too well without adjustment can itself produce:

A NEW PROBLEM.

This is why parenteral support should be reduced according to:

OBJECTIVE ABSORPTION AND HYDRATION.

ABSORPTION CAN CHANGE DRUG EXPOSURE

Another important concept:

If intestinal absorption improves:

ORAL MEDICATION ABSORPTION MAY ALSO CHANGE.

That may matter for medications with:

NARROW THERAPEUTIC WINDOWS.

This is a powerful reminder:

IMPROVING THE GUT CAN CHANGE THE PHARMACOLOGY OF EVERYTHING ELSE THE PATIENT TAKES.

THE CORE MECHANISM MAP

NUTRIENT EXPOSURE → INTESTINAL L CELLS → GLP-2 → GLP-2R → Indirect mediators:

IGF-1 / IGF-2

ERBB SIGNALING

KGF

VIP

NITRIC OXIDE → Potential:

CRYPT PROLIFERATION ↑

APOPTOSIS ↓

VILLUS HEIGHT ↑

BARRIER FUNCTION ↑

MESENTERIC BLOOD FLOW ↑

GASTRIC EMPTYING / SECRETION ↓ → Potential:

FLUID + NUTRIENT ABSORPTION ↑ → Potential:

INTESTINAL ADAPTATION + REDUCED PARENTERAL SUPPORT

The core concept is:

GLP-2 INCREASES THE FUNCTIONAL CAPACITY OF THE INTESTINE BY COORDINATING GROWTH, REPAIR, PERFUSION, AND ABSORPTION.

WHAT THIS MECHANISM MAY SUGGEST

Mechanistically, GLP-2 deserves interest in:

- short bowel syndrome
- post-resection adaptation
- intestinal barrier injury
- chemotherapy-associated mucositis
- intestinal ischemia-reperfusion
- intestinal failure
- severe malabsorption
- mucosal injury
- inflammatory bowel injury
- other states of insufficient functional absorptive surface

Its strongest validated therapeutic niche is:

SHORT BOWEL SYNDROME WITH PARENTERAL-SUPPORT DEPENDENCE.

WHAT THIS MECHANISM DOES NOT PROVE

GLP-2 biology does not prove that it:

- heals every GI disorder
- cures inflammatory bowel disease
- treats IBS simply because the gut is involved
- treats food sensitivity
- repairs intestinal tissue without addressing the underlying injury
- causes cancer
- treats every case of “leaky gut”
- replaces the missing intestine
- corrects SIBO
- should be used for every malabsorption syndrome
- is interchangeable with teduglutide
- is automatically safe in every proliferative context

Again:

INTESTINAL DYSFUNCTION ≠ ONE BIOLOGICAL PROBLEM.

THE EVIDENCE, POTENTIAL APPLICATIONS, AND LIMITATIONS

ENDOGENOUS PHYSIOLOGY

STRONG

GLP-2 is a well-characterized endogenous:

INTESTINAL L-CELL HORMONE.

Its roles in:

- mucosal growth
- barrier integrity
- gastric regulation
- absorption
- blood flow

are firmly established.

MECHANISTIC EVIDENCE

SUBSTANTIAL

The GLP-2R pathway is well characterized, even though many epithelial effects occur through:

INDIRECT LOCAL MEDIATORS.

Important downstream systems include:

- IGF signaling
- ErbB ligands

KGF

VIP

nitric oxide.

HUMAN STRUCTURAL EVIDENCE

STRONG

Teduglutide treatment has increased:

- villus height
- mucosal mass
- plasma citrulline

in human SBS studies.

This directly supports:

THE INTESTINOTROPHIC MECHANISM.

HUMAN FUNCTIONAL EVIDENCE

STRONG IN SBS-IF

Teduglutide has repeatedly reduced:

PARENTERAL FLUID / NUTRITION REQUIREMENTS

in randomized and long-term studies.

That is especially important because:

STRUCTURE → FUNCTION

has been demonstrated.

• Research

SHORT BOWEL SYNDROME

This is the defining clinical application.

The core problem is:

NOT ENOUGH FUNCTIONAL INTESTINE.

GLP-2 therapy attempts to:

MAXIMIZE THE CAPABILITY OF WHAT REMAINS.

That is a very precise therapeutic objective.

PARENTERAL NUTRITION REDUCTION

The pivotal clinical evidence shows that teduglutide can reduce:

PARENTERAL SUPPORT.

In the randomized STEPS trial:

• 63%

• of treated patients achieved at least a 20% reduction

versus:

• 30%

with placebo.

Again:

that is:

CLINICALLY MEANINGFUL ABSORPTIVE IMPROVEMENT.

ENTERAL AUTONOMY

Some patients can eventually become:

INDEPENDENT OF PARENTERAL SUPPORT.

This does not occur in everyone.

But long-term studies demonstrate that it is:

POSSIBLE IN SELECTED PATIENTS.

That is perhaps the ultimate functional endpoint:

THE REMAINING GUT TAKES OVER ENOUGH WORK TO ELIMINATE IV DEPENDENCE.

DIARRHEA / HIGH OUTPUT

GLP-2-related therapy can reduce:

• stool output

• ostomy output

• fluid losses

through:

INCREASED ABSORPTION + ALTERED SECRETION / MOTILITY.

In earlier metabolic-balance studies, teduglutide reduced diarrhea output by roughly 700 g/day and reduced fecal energy losses.

Again:

this is the difference between:

SYMPTOM SUPPRESSION

and:

CHANGING THE ABSORPTIVE PHYSIOLOGY CAUSING THE SYMPTOM.

INTESTINAL FAILURE

Short bowel syndrome and intestinal failure are related but not identical.

A patient can have:

SHORT BOWEL

without requiring:

PARENTERAL SUPPORT.

Intestinal failure means the GI tract cannot absorb enough:

FLUID / ELECTROLYTES / NUTRIENTS

to maintain health without:

IV SUPPORT.

That is the phenotype where teduglutide's clinical evidence is strongest.

CHEMOTHERAPY-ASSOCIATED MUCOSITIS

Chemotherapy can damage rapidly dividing intestinal epithelial cells.

That can cause:

- mucosal breakdown
- diarrhea
- malabsorption
- pain
- infection risk

Because GLP-2 promotes:

EPITHELIAL SURVIVAL + REGENERATION,

the pathway is mechanistically compelling.

Preclinical evidence supports this concept.

But this application does not have the same clinical maturity as:

SBS-IF.

INFLAMMATORY BOWEL DISEASE

GLP-2 has strong barrier and repair biology.

That may theoretically support:

MUCOSAL RECOVERY.

But Crohn's disease and ulcerative colitis involve:

IMMUNE DYSREGULATION.

So GLP-2 may eventually fit best as:

REPAIR SUPPORT

rather than:

PRIMARY IMMUNE CONTROL.

Again:

REPAIR THE WALL

and:

STOP THE ATTACK

are not necessarily the same therapy.

CELIAC DISEASE

Celiac disease causes:

IMMUNE-MEDIATED VILLOUS INJURY.

That makes GLP-2 biology superficially appealing.

But the fundamental treatment remains:

REMOVE THE GLUTEN-DRIVEN IMMUNE TRIGGER.

A trophic peptide cannot compensate indefinitely for:

CONTINUED IMMUNE DESTRUCTION.

Again:

DRIVER BEFORE REPAIR SIGNAL.

RADIATION ENTERITIS

Radiation can damage:

rapidly proliferating intestinal epithelium.

That makes GLP-2 mechanistically interesting in:

POST-RADIATION MUCOSAL RECOVERY.

Again:

the translational evidence remains far less mature than:

SHORT BOWEL SYNDROME.

INTESTINAL ISCHEMIA

GLP-2 increases:

INTESTINAL BLOOD FLOW

and supports:

MUCOSAL SURVIVAL.

This makes it biologically interesting in ischemic injury.

But:

AN OCCLUDED ARTERY STILL REQUIRES RESTORATION OF BLOOD FLOW.

Peptide support cannot substitute for:

SOURCE CONTROL OF ISCHEMIA.

GLP-2 IN OBESITY RESEARCH

Interestingly, newer research has also explored:

GLP-2R SIGNALING IN OBESITY AND METABOLIC CONTROL.

GLP-2R expression exists outside the intestine, including selected CNS and metabolic tissues, and recent work is exploring whether antagonizing or otherwise manipulating the pathway could influence obesity biology.

This is a reminder that:

A PEPTIDE'S BEST-KNOWN ORGAN MAY NOT BE ITS ONLY BIOLOGICAL DOMAIN.

But this is still a much earlier research area than:

INTESTINAL ADAPTATION.

WHAT WE KNOW

GLP-2 is a 33-amino-acid peptide derived from proglucagon.

It is secreted primarily by intestinal L cells.

GLP-1 and GLP-2 are commonly co-secreted but have very different dominant physiological roles.

GLP-2 primarily supports intestinal growth, absorption, barrier integrity, blood flow, and adaptation.

Its receptor is GLP-2R, a GPCR expressed in selected intestinal neural, endocrine, and stromal-related cells.

Many of GLP-2's epithelial growth effects are indirect rather than occurring through direct receptor activation on proliferating crypt epithelial cells.

GLP-2 increases crypt-cell proliferation and reduces epithelial apoptosis.

It increases villus height and mucosal mass.

It improves intestinal barrier function.

It increases mesenteric blood flow.

It can slow gastric emptying and reduce gastric secretion.

Together, these effects can increase nutrient and fluid absorption.

Native GLP-2 is rapidly degraded by DPP-4.

Teduglutide is a DPP-4-resistant GLP-2 analog developed to extend receptor activation.

Teduglutide has strong human clinical evidence in short bowel syndrome with intestinal failure.

In the pivotal STEPS trial, 63% of patients receiving teduglutide achieved at least a 20% reduction in parenteral-support volume versus 30% receiving placebo.

Long-term treatment can produce continued adaptation, and selected patients can eventually achieve independence from parenteral support.

Teduglutide is an FDA-approved GLP-2 analog for adults and pediatric patients at least 1 year old with short bowel syndrome who depend on parenteral support.

GLP-2's trophic biology also creates interest in mucosal injury, IBD, chemotherapy mucositis, ischemia, and barrier dysfunction, but these uses do not have the same level of human therapeutic validation.

Because GLP-2 promotes intestinal growth, pre-existing abnormal proliferative tissue requires appropriate consideration and surveillance rather than the simplistic conclusion that GLP-2 itself “causes cancer.”

WHAT WE THINK MAY BE HAPPENING

GLP-2 may function as:

THE INTESTINE'S “BUILD MORE CAPACITY” SIGNAL.

Food enters the gut. → **L cells detect:**

NUTRIENT AVAILABILITY. → **GLP-2 is released.** → **The peptide tells the intestine:**

NUTRIENTS ARE HERE - INCREASE YOUR ABILITY TO HANDLE THEM. → **Blood flow increases.** → **Absorptive tissue is supported.** → **Crypt cells proliferate.** → **Villi become larger.** → **Barrier function improves.** → **Transit and gastric delivery slow.** → **The system extracts:**

MORE FROM WHAT PASSES THROUGH IT.

After massive bowel loss:

this becomes especially powerful.

The body has:

LESS INTESTINE.

GLP-2 cannot:

CREATE METERS OF NEW BOWEL.

But it can potentially make the remaining intestine:

THICKER

BETTER PERFUSED

MORE ABSORPTIVE

and:

MORE FUNCTIONALLY EFFICIENT.

That may be the best conceptual definition of:

INTESTINAL ADAPTATION.

WHAT REMAINS CONTEXT-DEPENDENT

Important questions include:

Which intestinal cell populations are most important for GLP-2 action in humans?

How much growth depends on IGF-1 versus IGF-2?

How much depends on ErbB ligands?

What determines individual GLP-2R responsiveness?

Which SBS anatomy predicts the best response?

How important is colon continuity?

How important is residual ileum?

Why are some patients early responders and others delayed responders?

What predicts complete enteral autonomy?

How much response continues beyond two or three years?

Can shorter-acting or tissue-selective GLP-2 agonists provide different benefits?

Can GLP-2 repair inflammatory mucosal injury without worsening unwanted proliferation?

Can GLP-2 help chemotherapy-induced mucositis in humans?

Which barrier-dysfunction phenotypes genuinely reflect insufficient trophic signaling?

How should GLP-2 be combined with GLP-1 or other gut-hormone therapies?

Could tissue-selective GLP-2 antagonism eventually have a role in obesity?

How does the microbiome modify GLP-2 release and response?

Does altered GLP-2 signaling contribute meaningfully to obesity or metabolic disease?

How should improved oral-drug absorption be monitored during therapy?

Which biomarkers best reflect meaningful mucosal adaptation?

How should proliferative surveillance be individualized?

Again:

these questions define the move from:

INTESTINAL GROWTH SIGNAL

to:

PRECISION INTESTINAL REHABILITATION.

THE PRAXIS LENS

DO NOT BEGIN WITH GLP-2

Begin with:

WHAT PART OF INTESTINAL FUNCTION IS ACTUALLY FAILING?

Then:

PHYSIOLOGY

PATTERN → **MECHANISM** → **EVIDENCE** → **RISK** → **MONITORING** → **DECISION**

PHYSIOLOGY

Healthy intestinal function requires:

- adequate surface area
- intact villi
- normal epithelial permeability
- appropriate transit time
- healthy crypt renewal
- adequate perfusion
- digestive capacity
- controlled secretion

GLP-2 appears especially relevant to:

STRUCTURAL + ABSORPTIVE CAPACITY.

PATTERN

What is actually present?

short bowel syndrome?

intestinal failure?

high-output ostomy?

malabsorption?

mucosal injury?

inflammatory disease?

increased permeability?

rapid transit?

Again:

“GUT PROBLEM” IS NOT A MECHANISM.

MECHANISM

Does GLP-2 biology match:

THE DOMINANT BOTTLENECK?

If the patient cannot absorb because:

MOST OF THE SMALL BOWEL IS GONE,

GLP-2 is:

HIGHLY MECHANISTICALLY RELEVANT.

If malabsorption is caused by:

ACTIVE CELIAC DISEASE,

the immune trigger must be removed.

If diarrhea is caused by:

C. DIFFICILE,

treat:

THE INFECTION.

If barrier injury persists because of:

ONGOING NSAID EXPOSURE,

remove:

THE DRIVER.

Again:

REPAIR SIGNAL DOES NOT REPLACE SOURCE CONTROL.

EVIDENCE

Ask:

WHAT APPLICATION ARE WE DISCUSSING?

Short bowel syndrome with parenteral dependence?

STRONG HUMAN RCT + CLINICAL EVIDENCE.

Barrier protection?

STRONG PHYSIOLOGY + PRECLINICAL EVIDENCE.

Chemotherapy mucositis?

PROMISING PRECLINICAL EVIDENCE.

Generic “gut healing”?

TOO NONSPECIFIC.

Again:

EVIDENCE CLASS MATTERS.

RISK

The risk discussion should follow:

THE MECHANISM.

Important considerations include:

- fluid overload as absorption improves
- biliary or pancreatic complications
- growth of pre-existing intestinal polyps or abnormal tissue
- intestinal obstruction in susceptible anatomy
- altered oral-medication absorption
- inappropriate use where mucosal growth is not the actual problem

The FDA label therefore includes colonoscopic / intestinal-polyp surveillance and other monitoring around teduglutide therapy.

Again:

this is:

MECHANISM-BASED MONITORING.

MONITORING

Monitoring should follow:

THE ABSORPTIVE HYPOTHESIS.

FLUID BALANCE

- urine output
- edema
- parenteral-fluid requirements
- thirst
- body weight

NUTRITION

- parenteral-calorie requirements
- oral / enteral intake
- weight
- micronutrient status
- nutritional biomarkers

GI FUNCTION

- stool or ostomy output
- stool consistency
- abdominal symptoms
- transit pattern

STRUCTURAL / SAFETY

where appropriate:

- colonoscopy
- polyp surveillance
- biliary / pancreatic laboratory markers
- obstruction symptoms

FUNCTION

- fewer infusion days
- reduced IV volume
- improved independence
- quality of life

Again:

the best outcome is:

THE GUT DOING MORE WORK.

THE PRAXIS 5

MECHANISM

GLP-2 is primarily:

AN INTESTINOTROPHIC + PRO-ABSORPTIVE HORMONE.

Its major biological outputs include:

MUCOSAL GROWTH + BARRIER SUPPORT + BLOOD FLOW + ABSORPTION.

EVIDENCE

Endogenous physiology:

STRONG.

Mechanistic evidence:

SUBSTANTIAL.

Human structural evidence:

STRONG.

Human SBS therapeutic evidence:

STRONG.

Other GI repair applications:

EARLIER / APPLICATION-DEPENDENT.

RISK

The major conceptual mistake is:

ASSUMING MORE INTESTINAL GROWTH IS ALWAYS DESIRABLE.

In healthy adapting mucosa:

it may be useful.

In pre-existing abnormal proliferative tissue:

it may have a different meaning.

Again:

TISSUE CONTEXT MATTERS.

MONITORING

Monitor:

ABSORPTION + OUTPUT + NUTRITION + FLUID STATUS + STRUCTURAL SAFETY.

If the hypothesis is:

MORE FUNCTIONAL BOWEL,

then:

PARENTERAL DEPENDENCE SHOULD FALL OR INTESTINAL FUNCTION SHOULD OBJECTIVELY IMPROVE.

PATIENT CONTEXT

A patient with:

SHORT BOWEL SYNDROME AFTER MASSIVE RESECTION

is not identical to:

someone with:

IBS.

A patient with:

HIGH-OUTPUT JEJUNOSTOMY

is not identical to:

someone with:

CELIAC DISEASE.

A patient with:

SEVERE PARENTERAL-DEPENDENT INTESTINAL FAILURE

is not identical to:

someone who says:

“MY GUT FEELS INFLAMED.”

Same peptide pathway.

Different:

INTESTINAL PROBLEM.

SEVEN QUESTIONS TO ASK BEFORE GLP-2

1. WHAT PART OF INTESTINAL FUNCTION IS ACTUALLY FAILING?

surface area?

absorption?

barrier?

transit?

secretion?

mucosal repair?

2. WHY IS IT FAILING?

bowel resection?

inflammation?

infection?

immune injury?

ischemia?

medication?

3. DOES GLP-2'S INTESTINOTROPHIC BIOLOGY MATCH THE BOTTLENECK?

This is the central mechanistic question.

4. ARE WE DISCUSSING NATIVE GLP-2 OR A LONG-ACTING ANALOG SUCH AS TEDUGLUTIDE?

Pharmacokinetics matter.

5. WHAT TYPE OF EVIDENCE SUPPORTS THIS APPLICATION?

physiology?

animal injury model?

human SBS trial?

established clinical therapy?

6. WHAT WILL WE MONITOR?

stool / ostomy output?

parenteral volume?

nutrient absorption?

hydration?

mucosal / structural safety?

7. WHAT WOULD DEFINE SUCCESS?

Not:

“THE GUT FELT BETTER.”

But:

THE INTESTINE ABSORBED MORE, LOST LESS, REQUIRED LESS EXTERNAL SUPPORT, OR DEMONSTRATED OBJECTIVE IMPROVEMENT IN THE SPECIFIC FUNCTION BEING TARGETED.

KEY TAKEAWAYS

GLP-2 is a 33-amino-acid proglucagon-derived intestinal hormone.

It is secreted primarily by enteroendocrine L cells.

GLP-1 and GLP-2 are co-secreted but perform very different dominant physiological jobs.

GLP-1 is centered more strongly on glucose, insulin, appetite, and gastric regulation.

GLP-2 is centered more strongly on intestinal structure and absorptive capacity.

GLP-2 acts through the GLP-2 receptor.

GLP-2R is expressed on selected intestinal neural, endocrine, and stromal-related cells rather than simply on every proliferating crypt cell.

That means many of GLP-2's effects are indirect.

Important secondary mediators include IGF-1, IGF-2, ErbB ligands, KGF, VIP, and nitric oxide.

GLP-2 promotes crypt-cell proliferation.

It reduces epithelial apoptosis.

It increases villus height and mucosal mass.

It improves intestinal barrier function.

It increases mesenteric blood flow.

It can slow gastric emptying and reduce gastric secretion.

Together these actions increase the functional capacity of the intestine.

Native GLP-2 is rapidly degraded by DPP-4.

Teduglutide was engineered to resist this degradation and prolong GLP-2 receptor activation.

Teduglutide has strong human clinical evidence in short bowel syndrome with intestinal failure.

In the pivotal STEPS study, 63% of teduglutide-treated patients achieved at least a 20% reduction in parenteral support compared with 30% of placebo-treated patients.

Long-term therapy can produce continued reductions in parenteral support.

Selected patients can eventually achieve enteral autonomy.

This makes GLP-2 one of the clearest examples in peptide medicine where mechanism, tissue remodeling, and a meaningful clinical outcome line up.

Teduglutide is clinically established peptide medicine rather than merely an experimental peptide pathway.

• GLP-2 should not be reduced to a generic “gut-healing peptide.”

Its strongest identity is intestinal adaptation and absorption.

Barrier support is part of that biology, but “leaky gut” is not a sufficient diagnosis or indication.

GLP-2-related research in inflammatory bowel injury, mucositis, ischemia, and other barrier disorders is biologically interesting but less clinically mature than the SBS evidence.

Because GLP-2 is a trophic signal, abnormal proliferative context matters.

The evidence does not support the simplistic claim that GLP-2 causes cancer.

But pre-existing abnormal intestinal tissue requires appropriate consideration because a growth-promoting signal can have different effects in normal versus neoplastic tissue.

• The best question is not “does GLP-2 heal the gut?”

The better question is “what part of intestinal function has been lost, is inadequate mucosal surface, barrier integrity, perfusion, or absorptive capacity actually the bottleneck, does GLP-2 biology address that failed step, and can improved structure be translated into objectively better intestinal function?”

THE BOTTOM LINE

GLP-2 may be one of the most important peptides in the Gut & Barrier section because it teaches us that:

THE INTESTINE IS NOT FIXED.

It can:

ADAPT.

After major bowel loss, the body does not simply accept:

“THERE IS LESS INTESTINE NOW.”

The remaining bowel attempts to become:

MORE CAPABLE.

Villi can grow.

Crypt proliferation can increase.

Transport can improve.

Blood flow can increase.

Transit can change.

Secretions can change.

And GLP-2 is one of the central signals coordinating:

THAT ADAPTATION.

So the biological sequence becomes:

NUTRIENT EXPOSURE

L-CELL SIGNALING → GLP-2 → GLP-2R → Local mediators → MUCOSAL GROWTH

BARRIER SUPPORT

BLOOD FLOW

ABSORPTION → MORE FUNCTION FROM THE SAME LENGTH OF BOWEL

That is the central concept.

And teduglutide provides perhaps the most compelling translation of that mechanism.

The patient begins with:

NOT ENOUGH FUNCTIONAL INTESTINE TO SURVIVE WITHOUT IV SUPPORT.

Then GLP-2 receptor activation increases:

THE CAPACITY OF WHAT REMAINS.

And for many patients:

PARENTERAL REQUIREMENTS FALL.

For some:

they eventually become:

INDEPENDENT OF PARENTERAL SUPPORT.

That is not:

A SURROGATE ENDPOINT.

That is:

FUNCTIONAL PHYSIOLOGY RESTORED ENOUGH TO CHANGE DAILY LIFE.

And that may be the best way to think about regenerative peptide medicine.

Not:

“MAKE TISSUE GROW.”

But:

“MAKE THE REMAINING SYSTEM FUNCTION BETTER.”

The Praxis question therefore becomes:

“WHAT intestinal capacity has been lost, is the limiting problem inadequate absorptive surface, mucosal integrity, perfusion, transit, or secretion, does GLP-2 signaling address that bottleneck, and can increasing structural capacity produce a measurable reduction in fluid loss, malabsorption, nutritional dependence, or parenteral support?”

That is the difference between:

CALLING GLP-2 A GUT-HEALING PEPTIDE

and:

UNDERSTANDING INTESTINAL ADAPTATION.

FINAL RECALL

BUILD	SUPPORT	VERIFY
GLP-2 coordinates mucosal growth and repair	**Barrier, perfusion, transit, and absorption improve together**	**Less output or parenteral support must prove functional benefit**

STOP MEMORIZING PEPTIDES. START UNDERSTANDING THE SYSTEM.

Praxis Peptide Institute provides educational information and is not a substitute for individualized medical diagnosis or treatment. GLP-2 is an endogenous proglucagon-derived intestinal hormone studied for effects involving mucosal growth, crypt proliferation, barrier integrity, mesenteric blood flow, gastric emptying, secretion, fluid absorption, nutrient absorption, and intestinal adaptation. Its best-established therapeutic translation is through the long-acting analog teduglutide in patients with short bowel syndrome who depend on parenteral support. Relevance depends on the specific cause of intestinal dysfunction, residual anatomy, absorptive capacity, inflammatory or proliferative context, fluid and nutritional status, concurrent medications, whether native GLP-2 or an analog is being considered, and whether structural adaptation translates into meaningful functional improvement.