



PRAXIS
PEPTIDE INSTITUTE

IGF-1

ADVANCED MECHANISM AND EVIDENCE GUIDE

NUTRIENT-SENSITIVE GROWTH FACTOR DOWNSTREAM OF GH AND WITHIN THE IGFBP SYSTEM
70 amino acids • GH-IGF axis • IGF1R • PI3K-AKT-mTOR • MAPK • IGFBPs • ALS • growth • glucose

MEMORY KEY: IGF-1 IS NOT JUST GH DOWNSTREAM: IT IS A LOCAL AND ENDOCRINE GROWTH SIGNAL GATED BY NUTRITION, IGFBPS, AND TISSUE CONTEXT.

Educational monograph • Foundational human physiology • Established replacement in severe primary deficiency • Context-dependent translation elsewhere

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	CELL = mechanistic ANIMAL = organism-level preclinical HUMAN = clinical translation	CORE DISCIPLINE 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 IGF-1; the remaining pages add mechanism, evidence, context, and nuance.

01	IDENTITY A 70-amino-acid growth factor produced systemically and locally; it is related to insulin but biologically distinct.
02	AXIS GH promotes hepatic IGF-1, but local IGF-1 can also act through autocrine and paracrine signaling.
03	TARGET IGF1R is a receptor tyrosine kinase that engages PI3K-AKT-mTOR and RAS-RAF-MEK-ERK programs.
04	GATE IGFBP-1 through IGFBP-6 and ALS regulate transport, half-life, storage, release, and receptor access.
05	PERMISSION Nutrition, insulin, liver capacity, inflammation, age, and endocrine state determine whether growth is permitted.
06	CLINICAL FIT Direct replacement is established for severe primary IGF-1 deficiency, not as a universal substitute for GH.
07	TRADEOFF The same growth, survival, and glucose-lowering biology can produce benefit or risk depending on tissue and context.
08	PRAXIS QUESTION Why is IGF-1 abnormal, where is the axis failure, what are the binding proteins doing, and did function improve safely?

ONE-SENTENCE MEMORY

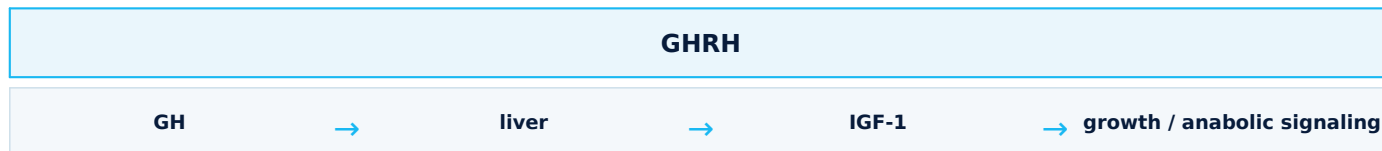
IGF-1 IS NOT JUST GH DOWNSTREAM: IT IS A LOCAL AND ENDOCRINE GROWTH SIGNAL GATED BY NUTRITION, IGFBPS, AND TISSUE CONTEXT.

UNDERSTAND THE PEPTIDE

IGF-1 - Insulin-Like Growth Factor-1 - is a 70-amino-acid peptide growth factor that sits downstream of growth hormone but also acts as an independent local signaling molecule in many tissues.

It is one of the most important growth and nutrient-integration signals in human physiology.

The simplest model is:



That is useful.

But incomplete.

Because IGF-1 is not simply:



Growth hormone and IGF-1 are:



GH can act directly.

IGF-1 can act:

- endocrinely
- paracrinely
- autocrinely

And circulating IGF-1 biology is heavily controlled by:



So the more complete model is:



- hepatic IGF-1 production ↑

and:



Meanwhile:

IGFBPs regulate:



That last part is crucial.

IGF-1 physiology is not simply:

TOTAL IGF-1 CONCENTRATION.

It is:

IGF-1 + IGFbps + ALS + IGF1R + NUTRITION + GH + INSULIN + TISSUE CONTEXT.

That is the actual system.

WHAT IS IGF-1?

IGF-1 is a:

70-AMINO-ACID SINGLE-CHAIN PEPTIDE.

Its structure is related to:

INSULIN.

That relationship is why it was named:

INSULIN-LIKE GROWTH FACTOR-1.

The two molecules belong to an evolutionarily related signaling family.

IGF-1 shares structural similarities with:

- insulin

IGF-2

and their receptors are related as well.

But:

IGF-1 IS NOT INSULIN.

And:

IGF1R IS NOT THE INSULIN RECEPTOR.

Their biology overlaps.

But their dominant physiological roles differ.

THE CORE IDENTITY

IGF-1



IGF1R



PI3K-AKT

- cell survival
- metabolism

- protein synthesis
- mTOR-related signaling

and:

RAS-MAPK

- cell proliferation
- growth

differentiation



Potential physiological outcomes:

LINEAR GROWTH**BONE FORMATION****MUSCLE PROTEIN ACCRETION****TISSUE GROWTH****CELL SURVIVAL****METABOLIC SIGNALING****Again:****IGF-1 IS A GROWTH-AND-NUTRIENT-CONTEXT SIGNAL.**

THE GH-IGF-1 AXIS

The classical endocrine pathway is:

Hypothalamu
s → GHRH → pituitary → GH → liver → IGF-1 → systemic growth signaling

But GH also acts directly on:

- adipose
- muscle
- liver
- other tissues

So:**GH**

does not simply exist to:

MAKE IGF-1.

Some effects of GH are:

IGF-1 INDEPENDENT.

And some IGF-1 is produced locally without functioning as a classical liver-derived endocrine hormone.

Again:**GH ≠ IGF-1.**

THE DIRECT VS INDIRECT GH MODEL

GH



DIRECT EFFECT

- lipolysis
- glucose / insulin effects
- protein metabolism

and:

INDIRECT EFFECT

IGF-1 production ↑



growth / anabolic effects

This distinction is extremely important.

ENDOCRINE IGF-1 VS LOCAL IGF-1

The liver produces most circulating endocrine IGF-1.

But many tissues also produce:

LOCAL IGF-1.

Examples include:

- skeletal muscle
- cartilage
- kidney
- bone
- brain
- reproductive tissues

Local IGF-1 can function through:

AUTOCRINE

or:

PARACRINE

signaling.

That means:

a tissue can produce IGF-1



and use it locally

without requiring a major rise in:

BLOOD IGF-1.

Again:

SERUM CONCENTRATION ≠ COMPLETE TISSUE SIGNALING.

THE LOCAL-SIGNAL MODEL

Muscle fiber / surrounding tissue → local IGF-1 → nearby IGF1R → growth / repair / adaptation

This is different from:

liver → circulating IGF-1 → distant tissues.

Again:

ENDOCRINE SIGNAL $\neq$ PARACRINE SIGNAL.

THE IGF-1 RECEPTOR - IGF1R

IGF-1 acts primarily through:

IGF1R.

IGF1R is a:

RECEPTOR TYROSINE KINASE.

This is fundamentally different from the GPCRs we have discussed in:

GLP-1

GHRH

- ghrelin
- somatostatin

IGF1R is structurally related to:

THE INSULIN RECEPTOR.

It exists as a preformed receptor complex containing:

- extracellular alpha subunits
- transmembrane beta subunits

When IGF-1 binds: → intrinsic tyrosine kinase activity increases → receptor autophosphorylation → IRS / SHC-related signaling → downstream pathways activate.

Again:

IGF-1 USES A TYROSINE-KINASE GROWTH-FACTOR RECEPTOR, NOT A CLASSICAL GPCR.

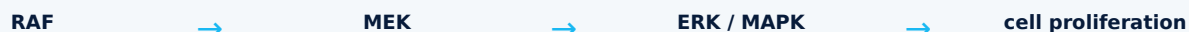
THE IGF1R SIGNALING PATHWAY



- cell survival
- metabolic regulation

and:

SHC / RAS



- growth
- differentiation

Again:

ONE RECEPTOR CAN FEED MULTIPLE DOWNSTREAM PROGRAMS.

- PI3K-AKT-mTOR

This pathway is especially important in:

ANABOLIC BIOLOGY.



and:

protein breakdown signaling may decrease.

This creates a mechanistic link between:

IGF-1

and:

MUSCLE PROTEIN ACCRETION.

But:

the presence of anabolic signaling does not mean:

IGF-1 AUTOMATICALLY BUILDS FUNCTIONAL MUSCLE IN EVERY CONTEXT.

More on that later.

MAPK SIGNALING

IGF1R can also activate:

RAS → RAF → MEK → ERK.

That pathway is strongly associated with:

- proliferation
- differentiation
- growth responses

So IGF-1 signaling contains both:

METABOLIC / SURVIVAL

and:

MITOGENIC

components.

Again:

ONE LIGAND CAN DRIVE DIFFERENT CELLULAR OUTCOMES DEPENDING ON THE DOWNSTREAM NETWORK.

IGF-1 AND INSULIN RECEPTOR OVERLAP

This is where the family becomes more interesting.

Because IGF1R and the insulin receptor are closely related:

they can form:

HYBRID RECEPTORS.

A hybrid receptor may contain:

- one IGF1R half
- one insulin-receptor half

These hybrid receptors can respond to IGF-family ligands differently from either receptor alone.

Again:

RECEPTOR BIOLOGY IS NOT ALWAYS ONE LIGAND → ONE RECEPTOR.

THE HYBRID-RECEPTOR MODEL

IGF1R

insulin receptor



hybrid receptor



ligand sensitivity differs

Potential:

IGF-1

- metabolic / proliferative signaling

This creates another reason why:

IGF-1 AND INSULIN BIOLOGY OVERLAP WITHOUT BEING IDENTICAL.

IGF-1 VS INSULIN

This distinction should be explicit.

INSULIN

Primary physiological identity:

NUTRIENT STORAGE / GLUCOSE CONTROL

Strong effects on:

- glucose uptake
- lipogenesis
- hepatic glucose suppression
- nutrient storage

IGF-1

Primary physiological identity:

GROWTH + SURVIVAL + ANABOLIC SIGNALING

Strong effects on:

- linear growth
- tissue development
- cell survival
- bone
- protein metabolism

There is overlap.

IGF-1 can:

LOWER GLUCOSE.

Insulin can:

PROMOTE GROWTH.

But:

their dominant physiological roles remain different.

IGF-1 CAN LOWER BLOOD GLUCOSE

This is clinically very important.

IGF-1 has:

INSULIN-LIKE METABOLIC ACTIVITY.

It can:

- increase glucose uptake
- reduce hepatic glucose output
- lower blood glucose

This is why pharmacologic recombinant IGF-1 can cause:

HYPOGLYCEMIA.

The current FDA labeling for mecasermin specifically warns of severe hypoglycemia, including hypoglycemic seizures, because IGF-1 has insulin-like glucose-lowering effects.

Again:

“INSULIN-LIKE” IS NOT JUST A NAME.

It has real metabolic consequences.

THE HYPOGLYCEMIA MODEL

IGF-1 exposure ↑



glucose uptake ↑

hepatic glucose output ↓



blood glucose ↓

If exposure exceeds:

nutrient availability



HYPOGLYCEMIA

This is why pharmacologic IGF-1 has to be understood differently from:

GH SECRETAGOGUES.

GH CAN RAISE GLUCOSE WHILE IGF-1 CAN LOWER IT

This creates an important endocrine tension.

GH

can:

- promote lipolysis
- reduce insulin sensitivity
- increase glucose availability

IGF-1

can:

- enhance glucose uptake
- produce insulin-like effects

So:

the GH-IGF-1 axis contains:

OPPOSING METABOLIC FORCES.

Again:

UPSTREAM HORMONE + DOWNSTREAM MEDIATOR CAN HAVE DIFFERENT GLUCOSE EFFECTS.

THE GLUCOSE-BALANCE MODEL

GH ↑



insulin resistance tendency ↑

Meanwhile:

IGF-1 ↑

- insulin-like glucose disposal ↑

Net:

depends on:

- | | |
|-------------------------|-----------------------|
| • hormone concentration | • nutritional state |
| • insulin sensitivity | • receptor expression |

Again:

THE AXIS IS A BALANCE.

IGF-1 AND GROWTH

IGF-1 is one of the body's dominant drivers of:

POSTNATAL LINEAR GROWTH.

At the growth plate:

IGF-1 influences:

- chondrocyte proliferation
- differentiation
- matrix production

This translates GH signaling into:

BONE LENGTHENING.

So:

GH

IGF-1



growth plate



long-bone growth.

Again:

GH INITIATES THE ENDOCRINE MESSAGE.

IGF-1 EXECUTES MUCH OF THE GROWTH PROGRAM.

THE GROWTH-PLATE MODEL



This is why severe IGF-1 deficiency can cause:

PROFOUND SHORT STATURE.

IGF-1 AND PRIMARY IGF-1 DEFICIENCY

One of the most important disease models is:

SEVERE PRIMARY IGF-1 DEFICIENCY.

In this condition:

GH may be:

NORMAL OR HIGH.

But IGF-1 remains:

VERY LOW.

Why?

Because:

the body cannot adequately translate:

GH → IGF-1 SIGNALING.

This can occur in:

GROWTH HORMONE INSENSITIVITY.

A classic example is:

LARON SYNDROME.

THE GH-RESISTANCE MODEL

Pituitary



GH ↑

But:

GH receptor / downstream signaling
impaired



IGF-1 ↓



growth impaired.

Now give more GH?



limited effect.

Because:

THE BOTTLENECK IS DOWNSTREAM OF GH.

This is one of the clearest examples of:

WHY LOCALIZING THE AXIS FAILURE MATTERS.

- MEcasermin - RECOMBINANT HUMAN IGF-1

The clinical translation of this biology is:

MECASERMIN.

Mecasermin is recombinant human:

IGF-1.

The FDA-approved product:

INCRELEX

is indicated for growth failure in children age 2 years and older with:

- severe primary IGF-1 deficiency

or GH gene deletion with neutralizing antibodies to GH.

This is not a general:

“GROWTH PEPTIDE.”

It is a highly specific example of:

REPLACING THE DOWNSTREAM SIGNAL WHEN THE UPSTREAM GH SIGNAL CANNOT PRODUCE IT.

THE REPLACEMENT LOGIC

GH adequate



IGF-1 inadequate



giving more GH does not solve it.

Therefore:

administer:

IGF-1 DIRECTLY.

Again:

BYPASS THE FAILED NODE.

This is textbook systems medicine.

MECASERMIN IS NOT A SUBSTITUTE FOR GH IN GENERAL GH DEFICIENCY

The current FDA label explicitly states that mecasermin is:

NOT A SUBSTITUTE FOR GH FOR APPROVED GH INDICATIONS.

Why?

Because if the problem is:

LOW GH

- and the GH receptor / IGF axis is intact,

then restoring GH may better recreate:

- GH effects
- IGF-1 generation
- physiological regulation

Again:

DOWNSTREAM REPLACEMENT $\neq$ UPSTREAM REPLACEMENT.

THE AXIS-LOCALIZATION PRINCIPLE

- Low growth velocity
- low IGF-1

does not automatically mean:

GIVE IGF-1.

Could be:

- | | |
|----------------------------------|-------------------|
| • GH deficiency | • GH resistance |
| • malnutrition | • liver disease |
| • hypothyroidism | • chronic illness |
| • genetic IGF signaling disorder | |

Again:

LOW IGF-1 IS A CLUE, NOT A COMPLETE DIAGNOSIS.

IGF-1 AND THE LIVER

The liver is the major source of:

CIRCULATING ENDOCRINE IGF-1.

GH stimulates hepatocytes



IGF-1 production ↑

But liver function matters.

If the liver is severely impaired:



IGF-1 may fall.

Again:

low IGF-1 can reflect:

ORGAN CAPACITY

rather than:

LOW GH.

THE LIVER-CAPACITY MODEL

GH normal



liver impaired



IGF-1 low.

If you interpret:

- low IGF-1

as:

- GH deficiency,

you may localize the problem incorrectly.

Again:

DOWNSTREAM MARKER ≠ UPSTREAM DIAGNOSIS.

IGF-1 AND NUTRITION

This is one of the most important concepts in the entire guide.

IGF-1 is highly:

NUTRITION SENSITIVE.

During severe calorie or protein restriction:

IGF-1 falls.

Even if:

GH rises.

This occurs partly because the liver becomes relatively:

GH RESISTANT.

So:

fasting



GH ↑

IGF-1 ↓

Again:

HIGH GH + LOW IGF-1 CAN BE NORMAL FASTING PHYSIOLOGY.

THE NUTRIENT-PERMISSION MODEL

GH says:

GROW.

But:

nutrient availability says:

WE DO NOT HAVE THE MATERIAL.

Liver response to GH falls.



IGF-1 falls.

This prevents the organism from entering:

ANABOLIC GROWTH MODE DURING ENERGY SCARCITY.

Again:

IGF-1 LINKS GROWTH TO NUTRIENT AVAILABILITY.

SIGNAL WITHOUT SUBSTRATE DOES NOT CREATE TISSUE

This deserves emphasis.

IGF-1 activates:

ANABOLIC SIGNALING.

But building tissue requires:

- amino acids
- minerals
- mechanical stimulus
- energy
- vitamins

So:

IGF-1 ↑

without:

- adequate substrate

does not magically create:

FUNCTIONAL TISSUE.

Again:

SIGNAL ≠ MATERIAL.

IGF-1 AND INSULIN

Insulin also helps regulate:

HEPATIC GH RESPONSIVENESS.

In states of severe insulin deficiency:

IGF-1 may fall.

This is particularly relevant in:

TYPE 1 DIABETES.

Low portal insulin can reduce:

- hepatic GH receptor expression
- IGF-1 generation

while GH can become elevated.

Again:

INSULIN IS PART OF THE GH-IGF-1 SYSTEM.

THE TYPE 1 DIABETES PATTERN

Insulin low in portal circulation → hepatic GH responsiveness ↓ → IGF-1 ↓ → negative feedback ↓ → GH ↑

Potential:

- lipolysis ↑
- metabolic instability ↑

Again:

ONE ENDOCRINE AXIS CAN DESTABILIZE ANOTHER.

- IGF-BINDING PROTEINS - IGFBPs

This is where IGF-1 becomes much more sophisticated.

There are six classical high-affinity IGF-binding proteins:

IGFBP-1

IGFBP-2

IGFBP-3

IGFBP-4

IGFBP-5

IGFBP-6

These proteins bind:

IGF-1

IGF-2

and regulate:

- | | |
|-------------------|-------------------|
| • half-life | • distribution |
| • receptor access | • tissue delivery |

Again:

MOST CIRCULATING IGF-1 IS NOT FREE.

It is:

BOUND.

TOTAL IGF-1 $\neq$ BIOAVAILABLE IGF-1

This distinction is fundamental.

Blood test says:

TOTAL IGF-1.

But biologic signaling depends on:

how much IGF-1 can actually:

REACH IGF1R.

IGFBPs can:

- protect IGF-1 from degradation
- transport it
- prevent immediate receptor binding
- release it locally under specific conditions

Again:

TRANSPORT + RESTRAINT CAN OCCUR AT THE SAME TIME.

IGFBP-3

IGFBP-3 is the dominant circulating IGF-binding protein.

Much of circulating IGF-1 exists in a large ternary complex:

IGF-1

IGFBP-3

ALS - ACID-LABILE SUBUNIT

This complex acts like a:

CIRCULATING RESERVOIR.

Recent reviews emphasize that most circulating IGFs are bound in binary or ternary complexes, with IGFBP-3/5 and ALS greatly prolonging IGF residence in the circulation.

THE TERNARY COMPLEX

IGF-1

IGFBP-3

ALS**large ~150-kDa
complex****remains largely
within circulation****IGF-1 protected from
rapid clearance****long circulating
reservoir.**

Without binding:

IGF molecules can be cleared much faster.

With ALS-containing ternary complexes:

their effective circulating half-life is dramatically prolonged.

Again:

BINDING CAN INCREASE DURATION WHILE REDUCING IMMEDIATE RECEPTOR ACCESS.

ALS - ACID-LABILE SUBUNIT

ALS is produced mainly by:

THE LIVER.

Its synthesis is strongly:

GH DEPENDENT.

ALS binds:

IGF-1-IGFBP-3

or:

IGF-1-IGFBP-5

to form the:

TERNARY COMPLEX.

Its role is not primarily to:

SIGNAL THROUGH IGF1R.

It is to:

CONTROL IGF TRANSPORT AND HALF-LIFE.

A 2024 Nature Reviews Endocrinology review described ALS as a major regulator of endocrine IGF transport, bioavailability, postnatal growth, and metabolism.

THE RESERVOIR PRINCIPLE

Free IGF-1**short-lived**

- strong receptor accessibility

Bound IGF-1**long-lived**

- less immediately available

Therefore:**BIOAVAILABILITY AND HALF-LIFE TRADE OFF AGAINST EACH OTHER.****Again:****MORE BINDING IS NOT SIMPLY “LESS IGF.”**

It can mean:

MORE STABLE IGF RESERVOIR.

IGFBP-1

IGFBP-1 is particularly dynamic.

It is strongly influenced by:

INSULIN.

Insulin tends to suppress:

IGFBP-1.

During fasting:

insulin falls**IGFBP-1 can rise.**

This can reduce:

FREE IGF-1 ACTIVITY.**Again:**

the body can rapidly change:

IGF BIOAVAILABILITY

without changing total IGF-1 dramatically.

THE FASTING-IGFBP MODEL

Fasting → insulin ↓ → IGFBP-1 ↑ → free IGF activity ↓

Meanwhile:

total IGF-1 may also fall with prolonged nutritional deprivation.

Again:

THE SYSTEM REDUCES ANABOLIC SIGNALING DURING ENERGY SCARCITY THROUGH MULTIPLE LAYERS.

IGFBP PROTEOLYSIS

IGFBPs are not permanent cages.

Specific enzymes can cleave them.

Important examples include:

PAPP-A

and:

PAPP-A2.

These proteases can cleave selected IGFBPs and increase:

LOCAL IGF AVAILABILITY.

Modern reviews describe PAPP-A/PAPP-A2 as physiologic regulators of IGF signaling through selective IGFBP proteolysis.

Again:

THE BODY CAN STORE IGF IN A BOUND STATE, THEN RELEASE IT LOCALLY WHEN NEEDED.

THE LOCAL-RELEASE MODEL

IGF-1

bound to IGFBP → low immediate receptor access

Then:

PAPP enzyme cleaves IGFBP → IGF-1 released locally → IGF1R activation ↑

Again:

PROTEASE ACTIVITY CAN CONTROL GROWTH-FACTOR SIGNALING.

IGF-1 AND MUSCLE

IGF-1 is strongly associated with:

SKELETAL-MUSCLE ANABOLIC SIGNALING.

Potential actions include:

- AKT activation
- protein synthesis
- differentiation
- mTOR signaling
- satellite-cell biology
- muscle growth

This is why IGF-1 attracts enormous interest in:

- sarcopenia
- recovery
- sports
- muscle injury

But the human therapeutic story is much more complicated than:

IGF-1 BUILDS MUSCLE.

MUSCLE HYPERTROPHY IS MULTISIGNAL

Functional hypertrophy requires:

MECHANICAL TENSION

AMINO ACIDS

ENERGY

NEURAL DRIVE

ANABOLIC SIGNALING

IGF-1 contributes to:

THE SIGNAL.

But:

it is not all of the system.

Again:

GROWTH SIGNAL $\neq$ TRAINING ADAPTATION BY ITSELF.

THE MUSCLE MODEL

Resistance training → mechanical signaling → local growth factors → IGF / AKT / mTOR-related pathways → protein synthesis ↑

But if:

- no training
- no protein

no energy



the output differs.

Again:

BIOLOGICAL CONTEXT DETERMINES WHAT THE SIGNAL BUILDS.

LOCAL MUSCLE IGF-1

Exercise can alter:

LOCAL IGF-1 SIGNALING

within muscle.

This has led to discussion of:

MECHANOGROWTH FACTOR - MGF

as an alternative splice-related IGF-1 transcript concept.

That subject becomes complex quickly.

The important point for this guide is:

MUSCLE IGF SIGNALING IS NOT FULLY REPRESENTED BY SERUM IGF-1.

Again:

LOCAL ADAPTATION ≠ BLOOD LEVEL.

IGF-1 AND BONE

IGF-1 is also a major regulator of:

BONE GROWTH + BONE FORMATION.

It influences:

- | | |
|--------------------|-------------------|
| • osteoblasts | • chondrocytes |
| • matrix synthesis | • skeletal growth |

During childhood:

this supports:

LINEAR GROWTH.

In adults:

IGF-1 remains relevant to:

- bone remodeling
- bone mass
- tissue maintenance

Again:

GROWTH PLATE PHYSIOLOGY AND ADULT BONE REMODELING ARE DIFFERENT APPLICATIONS OF THE SAME SIGNAL.

IGF-1 AND CARTILAGE

IGF-1 stimulates:

- chondrocyte matrix synthesis
- proteoglycan production
- cartilage-related anabolic pathways

This has led to interest in:

CARTILAGE REPAIR.

But:

systemic IGF-1 is not an established regenerative solution for osteoarthritis.

Why?

Because OA involves:

- | | |
|----------------------|--------------------------|
| • mechanical load | • inflammation |
| • matrix degradation | • chondrocyte senescence |
| • subchondral bone | • joint biomechanics |

Again:

ANABOLIC CARTILAGE SIGNAL $\neq$ JOINT REGENERATION PROVEN.

IGF-1 AND THE BRAIN

IGF-1 also participates in:

- | | |
|---------------------|--------------------------------|
| • neuronal survival | • synaptic function |
| • neurodevelopment | • vascular-neural interactions |

It can cross or influence blood-brain interfaces through regulated mechanisms.

This has generated research into:

- | | |
|---------------------|---------------------|
| • neurodegeneration | • cognitive decline |
| • stroke recovery | • brain aging |

But:

IGF-1 is not an established general:

NEUROREGENERATIVE THERAPY.

Again:

NEUROTROPHIC BIOLOGY $\neq$ CLINICAL NEUROREGENERATION.

IGF-1 AND CARDIOVASCULAR BIOLOGY

IGF-1 affects:

- vascular cells
- cardiac muscle
- endothelial biology

Low or high IGF-1 associations have been studied in:

- cardiovascular disease
- aging
- mortality

But epidemiology is complex.

Again:

ASSOCIATION $\neq$ IDEAL THERAPEUTIC TARGET LEVEL.

This is especially important because IGF-1 often shows:

NONLINEAR / U-SHAPED RELATIONSHIPS

with health outcomes.

THE U-SHAPED IGF-1 PRINCIPLE

Too little IGF-1:

- growth failure
- reduced bone / muscle support
- possible metabolic consequences

Too much chronic signaling:

- acromegaly-associated tissue growth
- potential proliferative concerns
- hypoglycemic / soft-tissue effects depending exposure

Therefore:

the goal is not:

MAXIMUM IGF-1.

It is:

APPROPRIATE IGF-1 FOR AGE + PHYSIOLOGY + DISEASE CONTEXT.

IGF-1 AND ACROMEGALY

In acromegaly:

GH secretion is excessive.**IGF-1 rises.**

IGF-1 becomes one of the primary integrated biomarkers used to:

ASSESS DISEASE ACTIVITY.

This is useful because:

GH is pulsatile.

IGF-1 is more stable.

Again:

DOWNSTREAM INTEGRATED MARKER CAN BE MORE CLINICALLY USEFUL THAN A RANDOM UPSTREAM HORMONE.

IGF-1 AND GH DEFICIENCY

The opposite pattern can occur in GH deficiency:

GH output ↓**IGF-1 ↓**

But:

low IGF-1 alone is not enough to diagnose:

ADULT GH DEFICIENCY.

Because IGF-1 also falls with:

- age
- liver disease
- malnutrition
- chronic illness

Again:

LOW IGF-1 HAS MULTIPLE CAUSES.

SERUM IGF-1 SHOULD BE AGE ADJUSTED

IGF-1 varies dramatically across the lifespan.

It rises during:

- childhood
- puberty

then declines gradually with:

AGE.

So interpreting:

"IGF-1 = 150"

without age context is meaningless.

A value normal for:

- a 70-year-old
- may be abnormal for:
a teenager.

Again:

LAB RANGE MUST MATCH PHYSIOLOGICAL AGE.

IGF-1 Z-SCORES

Because IGF-1 depends strongly on:

- age
- sex
- assay

labs often provide:

STANDARD-DEVIATION SCORES / Z-SCORES.

This can be more useful than:

a raw number alone.

Again:

REFERENCE CONTEXT IS PART OF THE BIOMARKER.

ASSAY DIFFERENCES MATTER

IGF-1 measurement is technically challenging because:

IGFBPs bind the peptide strongly.

Modern assays attempt to separate or account for:

IGFBP INTERFERENCE.

Different laboratories can produce somewhat different:

REFERENCE RANGES.

Again:

DO NOT COMPARE RAW IGF-1 NUMBERS FROM DIFFERENT ASSAYS AS THOUGH THEY WERE IDENTICAL.

IGF-1 AND AGING

IGF-1 declines with age.

This has generated two apparently conflicting ideas.

- Idea 1

Low IGF-1 contributes to:

- sarcopenia
- reduced tissue repair
- frailty
- Idea 2

Lower IGF signaling may be associated with:

LONGEVITY

in some organisms and genetic models.

Both can be true.

Because:

growth signaling has:

TRADEOFFS.

THE GROWTH-LONGEVITY TRADEOFF

Higher IGF signaling:



growth

- reproduction
- anabolism

But:

possibly:

less emphasis on:

cellular stress resistance / longevity pathways.

Lower IGF signaling:



less growth

but:

potentially greater:

- stress-response / longevity signaling

in some models.

Again:

THE OPTIMAL SIGNAL FOR GROWTH IS NOT NECESSARILY THE OPTIMAL SIGNAL FOR MAXIMUM LIFESPAN.

IGF-1 AND LONGEVITY - DO NOT OVERSIMPLIFY

It would be wrong to say:

"HIGH IGF-1 SHORTENS LIFE."

It would also be wrong to say:

"HIGHER IGF-1 IS ANTI-AGING."

Human data are far more complex.

Outcomes depend on:

- age
- nutritional status
- genetics
- receptor sensitivity
- sex
- disease
- IGFbps

Again:

PATHWAY ASSOCIATION $\neq$ SIMPLE OPTIMAL NUMBER.

IGF-1 AND CANCER BIOLOGY

This topic requires careful framing.

IGF1R activates:

PI3K-AKT

MAPK

- survival signaling

Those are normal pathways used by healthy tissues.

Cancer cells can also:

CO-OPT THEM.

So elevated IGF signaling has been investigated in:

- breast cancer
- colorectal cancer
- prostate cancer
- other malignancies

But:

IGF-1 DOES NOT SIMPLY “CAUSE CANCER.”

The correct statement is:

IGF-1 IS A GROWTH / SURVIVAL SIGNAL THAT CAN PARTICIPATE IN TUMOR BIOLOGY WHEN MALIGNANT CELLS USE THE SAME PATHWAY.

Again:

NORMAL GROWTH SIGNAL $\neq$ CANCER CAUSE.

THE ONCOLOGY MODEL



Therefore:

high or pharmacologic IGF exposure may require:

ONCOLOGICAL CONTEXT.

The current INCRELEX label contraindicates use in patients with malignant neoplasia and includes a warning regarding malignant neoplasia.

Again:

GROWTH-SIGNAL CONTEXT MATTERS.

IGF1R-TARGETED CANCER THERAPY - WHY IT WAS HARD

Given IGF1R's role in tumor biology:

drug developers attempted:

IGF1R INHIBITION.

The idea made sense.

But broad clinical success was limited.

Why?

Because tumor signaling is:

REDUNDANT.

Cancer cells can shift toward:

- insulin receptor

EGFR

- HER family
- PI3K mutations
- MAPK pathways

Again:

BLOCKING ONE GROWTH PATHWAY MAY NOT DEFEAT A NETWORKED DISEASE.

This parallels many of the systems lessons in the peptide library.

IGF-1 AND HYPOGLYCEMIA - MECASERMIN

The major acute pharmacologic concern with direct IGF-1 therapy is:

HYPOGLYCEMIA.

The FDA label warns that severe hypoglycemia, including seizures, has occurred and instructs administration around food because of mecamermin's insulin-like effects.

This makes nutritional timing a:

MECHANISM-BASED SAFETY VARIABLE.

Again:

THE SIDE EFFECT FOLLOWS DIRECTLY FROM THE MOLECULE'S BIOLOGY.

IGF-1 AND LYMPHOID TISSUE GROWTH

Pharmacologic IGF-1 can also cause:

LYMPHOID TISSUE HYPERTROPHY.

Examples include:

- tonsillar enlargement
- adenoidal enlargement

The current label lists lymphoid tissue hypertrophy among important precautions and tonsillar hypertrophy among common adverse events.

Again:

A GROWTH FACTOR CAN STIMULATE TISSUE YOU DID NOT INTEND TO TARGET.

IGF-1 AND INTRACRANIAL HYPERTENSION

Mecasermin labeling also includes:

INTRACRANIAL HYPERTENSION.

Potential symptoms can include:

- headache
- visual changes
- nausea

Again:

not every adverse effect is obvious from:

THE TARGET ORGAN.

Whole-body growth-factor exposure can have:

SYSTEMIC CONSEQUENCES.

IGF-1 AND SLIPPED CAPITAL FEMORAL EPIPHYSIS

Rapid growth can create orthopedic stress.

The current INCRELEX label includes a warning for:

SLIPPED CAPITAL FEMORAL EPIPHYSIS - SCFE, updated in 2025.

Why is that mechanistically logical?

Growth accelerates. → growth plate changes rapidly. → mechanical forces continue. → vulnerable epiphysis may slip.

Again:

FASTER GROWTH CAN CREATE STRUCTURAL STRESS.

THE GROWTH-RATE PRINCIPLE

More growth signaling



faster tissue change

But:

supporting structures must adapt too.

Again:

GROWTH SPEED ITSELF CAN BECOME A RISK VARIABLE.

IGF-1 AND SCOLIOSIS

Mecasermin labeling also warns about:

PROGRESSION OF PREEXISTING SCOLIOSIS.

Again:

the drug is not necessarily causing the underlying scoliosis.

Rapid growth can:

REVEAL OR ACCELERATE AN EXISTING STRUCTURAL PATTERN.

This is a very different concept.

IGF-1 AND SOFT-TISSUE GROWTH

IGF signaling can affect:

- muscle
- lymphoid tissue
- connective tissue
- organ tissue

Therefore chronic excessive IGF-1 exposure can alter:

TISSUE SIZE.

This is readily observable in:

ACROMEGALY.

Again:

ANABOLISM IS NOT TISSUE SPECIFIC UNLESS THE DELIVERY IS TISSUE SPECIFIC.

IGF-1 AND CARDIAC TISSUE

IGF-1 can promote:

CARDIOMYOCYTE SURVIVAL / GROWTH SIGNALING.

That may sound beneficial.

But:

excess GH/IGF-1 signaling in acromegaly is associated with:

CARDIAC REMODELING.

Again:

MORE ANABOLIC SIGNAL $\neq$ BETTER CARDIAC FUNCTION AUTOMATICALLY.

Dose and duration matter.

IGF-1 AND KIDNEY

IGF-1 also interacts with:

- renal growth
- filtration physiology
- sodium handling

Again:

systemic growth-factor signaling touches:

MULTIPLE ORGANS.

This is why using IGF-1 as though it were:

A MUSCLE-SPECIFIC PEPTIDE

is biologically inaccurate.

IGF-1 AND SPORTS / BODYBUILDING

This is an area where mechanism is often oversimplified.

IGF-1 clearly activates:

ANABOLIC SIGNALING.

But human performance use is not equivalent to:

TREATING SEVERE PRIMARY IGF-1 DEFICIENCY.

Potential concerns include:

- hypoglycemia
- edema-related effects
- growth-sensitive disease context
- excessive tissue growth
- altered insulin sensitivity

And in competitive sport:

IGF-1 and related growth factors are:

ANTI-DOPING RELEVANT.

Again:

ANABOLIC MECHANISM $\neq$ VALIDATED PERFORMANCE THERAPY.

IGF-1 AND MUSCLE STRENGTH

Even if lean mass increases:

strength depends on:

- | | |
|---------------------|----------------------|
| • fiber quality | • neural recruitment |
| • tendon adaptation | • training |
| • energy | • motor learning |

Again:

MASS $\neq$ FORCE.

This is the same lesson seen with:

GH

- anamorelin
- Tesamorelin

IGF-1 VS GROWTH HORMONE

This comparison deserves a dedicated section.

GH

Produced by:

pituitary.

Receptor:

GHR.

Major direct effects:

- lipolysis
- insulin antagonism
- growth signaling

Also increases:

IGF-1.

IGF-1

Produced by:

liver + local tissues.

Receptor:

IGF1R.

Major effects:

- | | |
|-----------------|---------------------------|
| • growth | • protein synthesis |
| • cell survival | • insulin-like metabolism |

Again:

GH SIGNALS THE SYSTEM TO GROW.

IGF-1 EXECUTES MANY OF THE DOWNSTREAM GROWTH PROGRAMS.

GH VS IGF-1 IN GLUCOSE

GH:

tends to:

RAISE GLUCOSE / REDUCE INSULIN SENSITIVITY.

IGF-1:

can:

LOWER GLUCOSE.

Again:

the downstream mediator is not simply:

A COPY OF THE UPSTREAM HORMONE.

IGF-1 VS TESAMORELIN

Tesamorelin



GHRHR



endogenous GH ↑



endogenous IGF-1 ↑

This preserves:

MORE OF THE AXIS.

Direct IGF-1:



IGF1R



bypasses:

GHRH

- pituitary GH
- hepatic control to some degree

Again:

UPSTREAM STIMULATION ≠ DOWNSTREAM REPLACEMENT.

IGF-1 VS CJC-1295 / SERMORELIN / MODIFIED GRF

All those molecules primarily act:

UPSTREAM

through:

GHRHR

GH



IGF-1.

Direct IGF-1 acts:

DOWNSTREAM.

So:

a low IGF-1 result does not automatically mean:
either strategy is appropriate.

You first have to ask:

WHERE DID THE AXIS FAIL?

IGF-1 VS IGF-1 LR3

This distinction is especially important for the later guide.

Native human IGF-1:

- binds IGF1R
- strongly interacts with IGFBPs

IGF-1 LR3:

is a modified analog engineered to:

REDUCE IGFBP BINDING

and increase:

BIOLOGICAL AVAILABILITY / DURATION.

That changes:

THE ENTIRE PHARMACOLOGICAL PROFILE.

Again:

NATIVE IGF-1 EVIDENCE $\neq$ IGF-1 LR3 EVIDENCE.

We will treat LR3 separately.

IGF-1 VS IGF-1 DES

IGF-1 DES is an N-terminally truncated form:

DES(1-3) IGF-1.

It also has altered:

IGFBP INTERACTIONS

and can demonstrate different potency in experimental systems.

Again:

A SMALL SEQUENCE CHANGE CAN ALTER BINDING-PROTEIN PHARMACOLOGY DRAMATICALLY.

That will also receive its own guide.

- IGFBPs ARE NOT "INHIBITORS" IN THE SIMPLE SENSE

This is crucial.

If an IGFBP binds IGF-1:

receptor access may fall temporarily.

That sounds inhibitory.

But the binding protein can also:

- protect IGF-1
- extend its half-life
- transport it
- concentrate it in tissues

So:

IGFBP

can both:

RESTRAIN

and:

ENABLE

IGF signaling.

Again:

BINDING PROTEIN $\neq$ SIMPLE OFF SWITCH.

THE DELIVERY-RESERVOIR MODEL

IGF-1 free



available now

but:

cleared faster.

IGF-1 bound



less available now

but:

stored / transported longer.

Then:

local protease



binding protein cleaved



IGF released.

Again:

BIOAVAILABILITY CAN BE TIME-DEPENDENT.

IGF-1 AND PREGNANCY

The IGF system is important in:

- fetal growth
- placental biology

But fetal growth relies heavily on:

IGF-2

as well as IGF-1.

The fetal system differs from the postnatal GH-driven endocrine axis.

Again:

LIFE STAGE CHANGES WHICH IGF SIGNAL DOMINATES.

IGF-1 AND PUBERTY

IGF-1 rises markedly during:

PUBERTY.

Why?

Growth hormone secretion increases.

Sex steroids increase.

Nutritional demand rises.

Growth velocity peaks.

Again:

PUBERTY IS A TEMPORARY HIGH-IGF PHYSIOLOGICAL STATE.

This is why age-adjusted interpretation is essential.

IGF-1 AND ESTROGEN

Estrogen alters:

GH-IGF-1 PHYSIOLOGY.

Importantly:

oral estrogen can reduce hepatic IGF-1 generation more than transdermal estrogen because of:

FIRST-PASS HEPATIC EFFECTS.

This is a useful example of:

ROUTE OF HORMONE DELIVERY ALTERING ANOTHER ENDOCRINE AXIS.

Again:

SAME HORMONE + DIFFERENT ROUTE = DIFFERENT SYSTEM EFFECT.

IGF-1 AND TESTOSTERONE

Androgens can interact with:

- GH secretion

IGF-1

- muscle anabolism

This partly explains the dramatic growth changes during:

PUBERTY.

Again:

ANABOLIC AXES INTERSECT.

IGF-1 AND THYROID

Thyroid hormone is necessary for:

NORMAL GROWTH.

Hypothyroidism can lower:

- growth velocity
- GH / IGF-related function

So:

low IGF-1 in a growing child may not be:

A PRIMARY IGF DISORDER.

Again:

ENDOCRINE SYSTEMS DO NOT OPERATE IN ISOLATION.

IGF-1 AND CHRONIC INFLAMMATION

Chronic inflammatory states can reduce:

IGF-1.

Mechanisms may include:

- cytokine effects
- GH resistance
- poor nutrition
- liver changes

Interestingly, ALS synthesis is also suppressed by inflammatory cytokines such as IL-1 β according to recent reviews.

Again:

INFLAMMATION CAN ALTER BOTH THE SIGNAL AND ITS TRANSPORT SYSTEM.

THE INFLAMMATION MODEL

Inflammation



GH responsiveness ↓

- IGF-1 production ↓

ALS ↓

nutrition often ↓



growth / anabolic physiology impaired

Again:**LOW IGF-1 MAY BE A SYSTEMIC ILLNESS SIGNAL.**

IGF-1 AND CRITICAL ILLNESS

Severe illness can create:

GH RESISTANCE.

GH may be elevated.

IGF-1 may be low.

Again:

this may represent:

ADAPTIVE METABOLIC PRIORITIZATION

rather than:

a simple hormone deficiency.

That distinction matters because:

trying to force the axis higher may not reproduce:

NORMAL PHYSIOLOGY.

IGF-1 AND “OPTIMAL LEVELS”

The internet often treats IGF-1 like:

a score.

Low?

Increase it.

High?

Great for muscle.

That is poor endocrinology.

IGF-1 must be interpreted relative to:

- age
- nutrition
- GH axis
- disease state
- sex
- liver function
- growth stage

Again:

THERE IS NO UNIVERSAL “BEST IGF-1” NUMBER.

THE CORE MECHANISM MAP

HYPOTHALAMUS



GHRH



PITUITARY GH



LIVER

IGF-1 ↑

and:

LOCAL TISSUES

local IGF-1
production



IGF-1



IGF1R



receptor tyrosine
kinase activation



PI3K → AKT → mTOR

PROTEIN SYNTHESIS / SURVIVAL / METABOLIC SIGNALING

RAS → RAF → MEK → ERK

PROLIFERATION / GROWTH / DIFFERENTIATION

Meanwhile:

IGFBP-1-6

ALS

regulate:

HALF-LIFE + TRANSPORT + RECEPTOR ACCESS

Potential physiological outcomes:

LINEAR GROWTH

BONE FORMATION

MUSCLE ANABOLIC SIGNALING

TISSUE SURVIVAL

GLUCOSE LOWERING

ORGAN GROWTH

The core concept is:

IGF-1 IS NOT MERELY A DOWNSTREAM GH NUMBER - IT IS A SYSTEMIC AND LOCAL GROWTH FACTOR WHOSE BIOLOGICAL EFFECT DEPENDS ON RECEPTOR SIGNALING, BINDING-PROTEIN CONTROL, NUTRIENT AVAILABILITY, TISSUE CONTEXT, AND THE LEVEL OF THE GH-IGF AXIS AT WHICH THE PROBLEM ACTUALLY OCCURS.

WHAT THIS MECHANISM MAY SUGGEST

IGF-1 biology is highly relevant to:

- severe primary IGF-1 deficiency
- linear growth
- muscle anabolism
- cartilage biology
- fasting physiology
- GH deficiency
- sarcopenia research
- growth hormone resistance
- pediatric endocrinology
- bone growth
- nutrient sensing
- insulin-related metabolism
- acromegaly
- aging biology
- neurobiology
- cancer biology
- IGFBP pharmacology

Its strongest physiological identity is:

A NUTRIENT-SENSITIVE GROWTH / SURVIVAL SIGNAL DOWNSTREAM OF GH AND WITHIN A MUCH LARGER IGF-BINDING-PROTEIN SYSTEM.

WHAT THIS MECHANISM DOES NOT PROVE

IGF-1 biology does not prove that:

- more IGF-1 is always better
- high IGF-1 automatically means better muscle growth
- IGF-1 is simply “active GH”
- higher IGF-1 always improves recovery
- IGF-1 alone rebuilds cartilage
- low IGF-1 from malnutrition should be corrected by peptide administration
- pharmacologic IGF-1 is appropriate for ordinary short stature
- low serum IGF-1 proves GH deficiency
- serum IGF-1 perfectly reflects local tissue IGF signaling
- GH and IGF-1 are interchangeable
- higher IGF-1 automatically improves strength
- IGF-1 alone regenerates nervous tissue
- low IGF-1 from liver disease proves an endocrine deficiency
- mecasermin substitutes for GH in all GH-deficient patients

every anabolic effect demonstrated in cells translates into better human performance

- IGF1R activation is harmless because it is physiological
- IGFBPs merely block IGF-1
- IGF-1 LR3 and IGF-1 DES can inherit native IGF-1 clinical evidence
- IGF signaling causes cancer by itself
- total IGF-1 equals free IGF-1

Again:

AXIS LOCATION + BINDING PROTEINS + NUTRITION + RECEPTOR SIGNALING + TISSUE CONTEXT MATTER.

THE EVIDENCE, POTENTIAL APPLICATIONS, AND LIMITATIONS

ENDOGENOUS PHYSIOLOGY

EXTREMELY STRONG

IGF-1 is a core physiological regulator of:

- postnatal growth
- tissue development
- nutrient-linked anabolic signaling

IGF1R BIOLOGY

EXTREMELY STRONG

IGF1R is a well-characterized receptor tyrosine kinase activating:

PI3K-AKT

- MAPK-related pathways

and interacting with insulin-receptor signaling.

IGFBP / ALS PHYSIOLOGY

EXTREMELY STRONG

Most circulating IGF is bound to IGFBPs, and a large portion is contained within:

IGF + IGFBP-3/5 + ALS TERNARY COMPLEXES.

This is essential to understanding:

- half-life
- bioavailability

transport.

SEVERE PRIMARY IGF-1 DEFICIENCY

VERY STRONG HUMAN CLINICAL EVIDENCE

Recombinant human IGF-1 - mecasermin - is FDA approved for long-term treatment of growth failure in children with severe primary IGF-1 deficiency or certain GH-gene-deletion patients with neutralizing GH antibodies.

GENERAL GH DEFICIENCY

DIRECT IGF-1 REPLACEMENT IS NOT THE STANDARD SUBSTITUTE FOR GH

The current mecasermin label explicitly states that it is not a substitute for GH for approved GH indications.

MUSCLE / PERFORMANCE

MECHANISTICALLY STRONG - THERAPEUTIC EVIDENCE MUCH MORE LIMITED

IGF-1 clearly participates in:

ANABOLIC MUSCLE SIGNALING.

But this does not establish systemic IGF-1 as a validated athletic-performance therapy.

BONE / LINEAR GROWTH

VERY STRONG

IGF-1 is a major mediator of:

- growth-plate biology
- skeletal development

especially during childhood and adolescence.

CARTILAGE REGENERATION

MECHANISTICALLY PLAUSIBLE - HUMAN THERAPEUTIC EVIDENCE LIMITED

IGF-1 can stimulate chondrocyte anabolic activity.

That does not establish:

SYSTEMIC IGF-1 AS A REGENERATIVE OA TREATMENT.

AGING / LONGEVITY

COMPLEX AND NONLINEAR

Both low and high IGF signaling may carry tradeoffs.

There is no simple human conclusion that:

MORE IGF-1 = LONGER / HEALTHIER LIFE

or:

LESS IGF-1 = BETTER LONGEVITY.

ONCOLOGY

STRONG PATHWAY INVOLVEMENT - CLINICALLY COMPLEX

IGF1R signaling can contribute to tumor growth / survival in selected contexts.

But broad IGF1R-targeted oncology strategies have not produced universal success.

Again:

PATHWAY IMPORTANCE $\neq$ EASY THERAPEUTIC TARGET.

- Research

GROWTH HORMONE RESISTANCE

This is the cleanest mechanistic use of direct IGF-1 replacement.

GH is present.



IGF-1 is not produced adequately.



replace:

THE MISSING DOWNSTREAM SIGNAL.**Again:****BYPASS THE FAILED RECEPTOR / SIGNALING NODE.****MUSCLE**

IGF-1 is mechanistically central to:

- protein synthesis
- satellite-cell biology
- hypertrophic signaling

But future research needs to distinguish:

- | | |
|---------------|-------------|
| • muscle mass | • lean mass |
| • strength | • function |

performance.

Again:**ANABOLIC SIGNAL ≠ FUNCTION.****SARCOPENIA**

IGF-1 is attractive because sarcopenia involves:

- low muscle mass
- reduced anabolic responsiveness

But older adults may also have:

- | | |
|----------------|---------------------------|
| • low activity | • low protein |
| • inflammation | • neurological limitation |

So:

IGF-1 signaling may be only:

ONE NODE.**BONE**

The biology is very strong.

Future targeted strategies may attempt to enhance:

LOCAL IGF SIGNALING

without creating excessive systemic exposure.

Again:**TISSUE-TARGETED ANABOLISM MAY BE MORE ATTRACTIVE THAN WHOLE-BODY GROWTH-FACTOR EXPOSURE.**

CARTILAGE

The same principle applies.

Local delivery could theoretically improve:

THERAPEUTIC INDEX.

But:

human structural outcomes remain the standard.

NEUROBIOLOGY

IGF-1's trophic biology is compelling.

But the central questions remain:

- delivery
- dose
- receptor access
- disease stage

unwanted peripheral effects.

AGING

Perhaps one of the most important questions is:

CAN WE PRESERVE THE BENEFICIAL TISSUE EFFECTS OF IGF SIGNALING WITHOUT CHRONICALLY MAXIMIZING GROWTH-SURVIVAL PATHWAYS?

That is a much better question than:

HOW DO WE RAISE IGF-1?

WHAT WE KNOW

IGF-1 is a 70-amino-acid peptide growth factor produced predominantly by the liver in the endocrine GH axis and locally by many tissues.

It signals primarily through the IGF-1 receptor, a receptor tyrosine kinase closely related to the insulin receptor.

IGF1R activates major intracellular pathways including PI3K-AKT and RAS-MAPK, thereby regulating protein synthesis, survival, proliferation, differentiation, and metabolic responses.

IGF-1 is therefore not simply a blood marker downstream of GH.

It is a major biologically active growth factor in its own right.

The liver is a major source of circulating endocrine IGF-1, but many tissues also produce IGF-1 locally.

This means serum IGF-1 cannot capture all tissue-level IGF activity.

Most circulating IGF-1 is bound rather than free.

The six classical IGF-binding proteins regulate IGF transport, half-life, and receptor access.

IGFBP-3 is especially important in the circulation.

A large fraction of postnatal circulating IGF exists in a ternary complex containing IGF-1 or IGF-2, IGFBP-3 or IGFBP-5, and the acid-labile subunit ALS.

This ternary complex acts as a stable circulating reservoir and markedly prolongs IGF half-life.

Therefore IGFBPs should not be viewed simply as inhibitors.

They can reduce immediate receptor access while simultaneously protecting, transporting, and preserving the ligand.

IGF availability can later be increased locally through proteolysis of binding proteins by enzymes such as PAPP-A and PAPP-A2.

This makes IGF-1 signaling a spatially and temporally regulated system.

IGF-1 is also highly nutrient sensitive.

Severe fasting, protein deficiency, liver disease, chronic illness, or impaired insulin physiology can lower IGF-1 even when GH is not deficient.

Therefore low IGF-1 does not automatically prove low GH.

In severe primary IGF-1 deficiency, however, the downstream defect can be profound enough that direct IGF-1 replacement becomes appropriate.

Mecasermin - recombinant human IGF-1 - is FDA approved for selected pediatric patients with severe primary IGF-1 deficiency or GH-gene deletion with neutralizing antibodies.

The label specifically states that mecasermin is not a substitute for GH for approved GH indications.

This perfectly illustrates axis localization.

If GH is absent but the downstream system is functional, replace or restore GH.

If GH is present but cannot generate adequate IGF-1 because the GH receptor pathway is defective, bypass that node and provide IGF-1 directly.

IGF-1 also has insulin-like metabolic effects.

Pharmacologic mecasermin can cause severe hypoglycemia, including seizures, which is why the FDA labeling specifically emphasizes administration in relation to food.

This is an important difference from GH, which tends to antagonize insulin and can raise glucose.

The GH-IGF axis therefore contains opposing metabolic influences.

IGF-1 is also a potent growth signal.

That is therapeutically useful in severe deficiency but creates predictable growth-related safety considerations, including lymphoid hypertrophy, intracranial hypertension, progression of preexisting scoliosis, and slipped capital femoral epiphysis during rapid growth.

Again:

THE BENEFIT AND THE RISK COME FROM THE SAME BIOLOGY.

WHAT WE THINK MAY BE HAPPENING

IGF-1 may be best understood as:

THE BODY ASKING TWO QUESTIONS AT THE SAME TIME:

IS THERE A GROWTH SIGNAL?

and:

ARE THERE ENOUGH RESOURCES TO ACT ON IT?

GH rises.

That is:

THE ENDOCRINE INSTRUCTION.

But if the patient is:

- starving,
- severely ill,
- protein deficient,
- or unable to support hepatic GH signaling,

then IGF-1 falls.

Why?

Because:

GROWTH IS EXPENSIVE.

It requires:

- amino acids
- lipids
- energy
- glucose
- minerals

The body should not launch a large anabolic program when:

ENERGY IS SCARCE.

So IGF-1 becomes partly:

A NUTRIENT-PERMISSION SIGNAL.

That helps explain the fasting paradox.

GH rises during fasting.

Why?

To mobilize fuel.

But IGF-1 falls.

Why?

Because:

THIS IS NOT THE TIME FOR GROWTH.

That separation allows GH to support:

FUEL MOBILIZATION

without fully activating:

THE GROWTH PROGRAM.

Then food returns.

Insulin rises.

Nutrient availability improves.

Hepatic GH sensitivity improves.

IGF-1 rises.

Now the system can move toward:

ANABOLISM.

That is much more elegant than:

GH HIGH = IGF-1 HIGH.

It means the axis is integrating:

HORMONAL INSTRUCTION + NUTRIENT PERMISSION.

Then the body adds another layer.

Most IGF-1 is not left floating freely.

It is packaged.

IGFBP-3.

ALS.

Ternary complex.

Why?

Because an insulin-like growth factor moving freely at high concentration would be:

POWERFUL AND SHORT-LIVED.

Instead the body creates:

A CONTROLLED RESERVOIR.

Then local tissues can release IGF activity when needed through:

BINDING-PROTEIN PROTEOLYSIS.

So the complete system is not:

GH

IGF-1

→

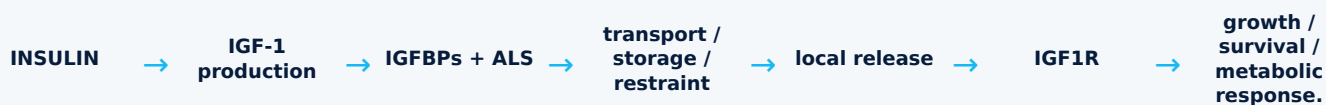
growth.

It is:

GH

NUTRITION

LIVER FUNCTION



That is:

A SYSTEM.

WHAT REMAINS CONTEXT-DEPENDENT

Important questions include:

- How much circulating IGF-1 versus local IGF-1 drives muscle adaptation?
- How much local IGF-1 contributes to systemic measurements?
- Which tissue-specific IGF-1 isoforms have meaningful physiological roles?
- How much does IGF-1 directly drive hypertrophy after resistance exercise?
- How much is downstream of mechanical mTOR signaling independent of IGF-1?
- Does increased serum IGF-1 meaningfully predict muscle gain?
- Does serum IGF-1 predict strength?
- How much does local IGFBP proteolysis determine muscle IGF signaling?
- Does PAPP-A activity change with exercise?
- Can local IGF release be therapeutically targeted?
- How much free IGF-1 actually circulates in humans?
- Is free IGF-1 more clinically informative than total IGF-1?
- Can free IGF-1 be measured reliably enough for routine use?
- How much does IGFBP-1 alter acute tissue response?
- How much does insulin-driven suppression of IGFBP-1 increase postprandial IGF activity?
- What is the physiologic importance of IGFBP-2?
- How important is IGFBP-5 in bone and muscle?
- How much of IGFBP biology is IGF dependent versus IGF independent?
- What does ALS contribute beyond half-life?
- Can ALS itself participate in cellular signaling?
- How important is inflammation-driven suppression of ALS?
- Can IGFBP-1 become a marker of GH action or systemic inflammation?
- Why do IGFBP-1 mutations cause only modest growth impairment despite large reductions in circulating IGF?
- How much local IGF compensates when circulating IGF falls?
- How does liver disease alter IGFBP distribution?
- How does renal disease alter IGF clearance?
- How should IGF-1 be interpreted in obesity?
- How much does hyperinsulinemia alter free IGF availability?
- How does insulin resistance change IGF1R signaling?
- How much cross-activation occurs through insulin receptors at pharmacologic IGF-1 concentrations?
- Which insulin-receptor isoform matters most?
- How important are IGF1R/insulin-receptor hybrid receptors clinically?
- Can receptor-hybrid abundance predict metabolic response?
- Can IGF-1 improve insulin sensitivity at physiologic concentrations?
- When does pharmacologic IGF-1 create unacceptable hypoglycemia?
- How should meal composition alter megestrol safety?
- Why do some patients experience severe hypoglycemia while others do not?
- Does baseline insulin sensitivity predict risk?

Can CGM improve safety during direct IGF-1 therapy?

How much does IGF-1 contribute to acromegaly complications independently of GH?

Which acromegaly complications correlate most strongly with IGF-1 normalization?

Is normalized IGF-1 sufficient if GH remains abnormal?

How does age change optimal IGF-1 exposure?

Does high-normal IGF-1 in older adults improve muscle or increase unwanted growth signaling?

Is low IGF-1 in aging adaptive?

Which longevity findings from worms / flies / mice translate to humans?

Can tissue-specific IGF reduction produce longevity benefits without frailty?

Can muscle IGF signaling be preserved while systemic proliferative signaling is reduced?

Is that biologically achievable?

Can IGF1R signaling be biased toward metabolic rather than mitogenic pathways?

Can ligand engineering separate PI3K-AKT from MAPK signaling?

Could tissue-targeted IGF analogs improve muscle or bone without systemic exposure?

Can bone-targeted IGF improve osteoporosis?

Can cartilage-targeted IGF aid OA?

How much cartilage degeneration is reversible even with strong anabolic signaling?

Can local IGF overcome chondrocyte senescence?

Does mechanical overload negate anabolic IGF benefit?

Can IGF improve tendon healing?

Does tendon strength increase proportionally or does growth outpace matrix organization?

Can IGF improve nerve regeneration?

What dose and delivery route would reach nervous tissue safely?

Does systemic IGF meaningfully cross the blood-brain barrier?

What role does local brain IGF play compared with circulating IGF?

Can IGF1R modulation improve Alzheimer's disease?

Could increased signaling worsen tumor risk in older patients?

How should prior malignancy affect IGF-based therapy?

Which tumors are most dependent on IGF1R?

Why did many IGF1R oncology strategies fail clinically?

Can biomarkers identify the tumors that truly depend on this pathway?

How much insulin-receptor compensation defeats IGF1R inhibition?

Can dual IGF1R / insulin-receptor inhibition be tolerated?

How does IGF-1 interact with estrogen signaling in breast tissue?

How does it interact with androgen signaling in prostate tissue?

What degree of physiological IGF variation actually changes cancer risk?

Is serum IGF-1 causal or merely correlated with nutritional / hormonal state?

Can growth-factor exposure be individualized by IGFBP profile?

How should IGF-1 Z-scores be integrated with symptoms and dynamic GH testing?

When does low IGF-1 justify further endocrine evaluation?

How should low IGF-1 in a calorie-restricted athlete be interpreted?

How should it be interpreted in RED-S?

Can restoring nutrition normalize IGF-1 without any peptide intervention?

How rapidly does IGF-1 recover after refeeding?

Can low IGF-1 serve as a marker of inadequate energy availability?

How do oral versus transdermal estrogens alter IGF-1 in clinical practice?

Can that effect be used therapeutically?

How does testosterone therapy alter GH-IGF-1 signaling?

Does combined androgen + GH signaling create synergistic tissue growth?

What are the long-term consequences?

How much of pediatric response to mecasermin is predicted by baseline IGF-1?

How much by age at treatment initiation?

How much growth potential is lost once epiphyses close?

Can direct IGF-1 therapy ever have a meaningful role after epiphyseal closure outside rare indications?

How should IGF-1 LR3 and DES be evaluated given their reduced binding-protein interaction?

Does reduced IGFBP binding increase efficacy or simply increase uncontrolled exposure?

What does longer systemic availability do to hypoglycemia risk?

Does decreased IGFBP regulation change tissue selectivity?

Can modified IGF analogs ever reproduce physiological compartmentalization?

Again:

these are the questions needed to move from:

GROWTH FACTOR

to:

PRECISION IGF-AXIS BIOLOGY.

THE PRAXIS LENS

DO NOT BEGIN WITH IGF-1

Begin with:

WHY IS THE GH-IGF AXIS ABNORMAL, WHERE IS THE FAILURE, AND IS IGF-1 ITSELF ACTUALLY THE LIMITING NODE?

Then:

PHYSIOLOGY

PATTERN



MECHANISM



EVIDENCE



RISK



MONITORING



DECISION

PHYSIOLOGY

Normal IGF-1 physiology requires:

- appropriate GH secretion
- intact hepatic signaling
- sufficient energy
- healthy liver function
- functional IGF1R
- functional GH receptors
- adequate insulin
- sufficient protein
- normal IGFBP / ALS transport
- appropriate tissue responsiveness

Its central identity is:

NUTRIENT-PERMISSIVE GROWTH SIGNALING.

PATTERN

What is actually present?

severe short stature?

low IGF-1?

GH deficiency?

GH resistance?

malnutrition?

liver disease?

sarcopenia?

acromegaly?

excessive growth signaling?

athlete with calorie restriction?

Again:

“LOW IGF-1” IS NOT A DIAGNOSIS.

MECHANISM

Where did the system fail?

Hypothalamus?

GHRH low.

Pituitary?

GH low.

GH receptor?

GH resistance.

Liver?

IGF-1 synthesis impaired.

Nutrition?

insufficient anabolic permission.

IGF1R?

downstream signaling abnormal.

Again:

THE TREATMENT DEPENDS ON THE LEVEL OF FAILURE.

EVIDENCE

Ask:

WHAT CLAIM ARE WE MAKING?

IGF-1 is a major human growth factor?

EXTREMELY STRONG.

IGF1R activates PI3K-AKT and MAPK signaling?

EXTREMELY STRONG.

IGFBPs / ALS regulate circulating IGF bioavailability?

EXTREMELY STRONG.

Direct recombinant IGF-1 can treat severe primary IGF-1 deficiency?

VERY STRONG HUMAN CLINICAL EVIDENCE.

Direct IGF-1 should replace GH in routine GH deficiency?

NO.

IGF-1 builds functional muscle in healthy adults simply because the pathway is anabolic?

NOT ESTABLISHED AS A GENERAL THERAPEUTIC CLAIM.

IGF-1 regenerates human cartilage?

NOT ESTABLISHED.

Higher IGF-1 improves longevity?

NOT ESTABLISHED.

Again:

KEEP THE CLAIM AT THE EVIDENCE LEVEL.

RISK

The central risk is:

UNCONTROLLED SYSTEMIC GROWTH-FACTOR EXPOSURE.

Mechanism-based concerns include:

- hypoglycemia
- lymphoid hypertrophy
- rapid-growth orthopedic complications
- growth-sensitive malignancy context
- soft-tissue growth
- intracranial hypertension
- progression of preexisting scoliosis

The current mecasermin labeling specifically includes these concerns.

Again:

THE SAME BIOLOGY THAT CREATES GROWTH CREATES GROWTH-RELATED RISK.

MONITORING

Monitoring should follow:

THE SPECIFIC IGF-1 HYPOTHESIS.

GROWTH

- height
- bone age
- growth velocity
- pubertal stage

GH-IGF AXIS

IGF-1

- age-adjusted Z-score
- GH testing where clinically appropriate
- IGFBP-3 when relevant

GLUCOSE

especially with direct IGF-1:

- fasting glucose
- symptomatic hypoglycemia
- CGM where clinically justified

ORTHOPEDIC

during rapid pediatric growth:

- hip / knee pain
- limp

- scoliosis progression

NEUROLOGICAL / OPHTHALMIC

if symptoms suggest intracranial hypertension:

- headache
- vision changes

SOFT TISSUE

- tonsillar / adenoidal hypertrophy
- airway symptoms

NUTRITION

- | | |
|--------------------|-----------------|
| • calorie adequacy | • protein |
| • liver function | • insulin state |

ONCOLOGICAL CONTEXT

where relevant:

- malignancy history
- appropriate surveillance

Again:

MONITOR THE SYSTEM THE GROWTH FACTOR IS CHANGING.

THE PRAXIS 5

MECHANISM

IGF-1's defining pathway is:

IGF-1 → IGF1R → PI3K-AKT-mTOR + RAS-MAPK → GROWTH / SURVIVAL / METABOLIC SIGNALING.

But its actual activity is shaped by:

IGFBPs + ALS + NUTRIENT STATE + GH + INSULIN.

Its central identity is:

REGULATED GROWTH-FACTOR SIGNALING.

EVIDENCE

Endogenous physiology:

EXTREMELY STRONG.

IGF1R signaling:

EXTREMELY STRONG.

IGFBP / ALS system:

EXTREMELY STRONG.

Severe primary IGF-1 deficiency treatment with mecasermin:

VERY STRONG.

Muscle / regeneration applications:

MECHANISTICALLY INTERESTING BUT FAR MORE LIMITED AS DIRECT HUMAN THERAPEUTIC EVIDENCE.

Longevity:

COMPLEX / NONLINEAR.

RISK

The biggest conceptual mistake is:

ASSUMING THAT BECAUSE IGF-1 IS ANABOLIC, MORE IS BETTER.

The second is:

TREATING LOW IGF-1 WITHOUT FINDING OUT WHY IT IS LOW.

- A malnourished patient
- with low IGF-1

needs:

NUTRITION.

- A GH-deficient patient

needs:

THE GH AXIS ADDRESSED.

- A GH-resistant patient

may require:

DOWNSTREAM THINKING.

Again:

SAME BIOMARKER. DIFFERENT PHYSIOLOGY.

MONITORING

Monitor:

THE TARGET PHENOTYPE + GLUCOSE + GROWTH RATE + AXIS MARKERS + TISSUE EFFECTS.

- If IGF-1 rises

but:

- the intended outcome does not improve,
more IGF-1 is not automatically:

THE ANSWER.

Again:

BIOCHEMICAL RESPONSE $\neq$ CLINICAL SUCCESS.

PATIENT CONTEXT

A child with:

SEVERE PRIMARY IGF-1 DEFICIENCY

is very different from:

a healthy adult bodybuilder.

A patient with:

GH RESISTANCE

is different from:

someone with:

PITUITARY GH DEFICIENCY.

A patient with:

LOW IGF-1 FROM MALNUTRITION

is different from:

someone with:

GENETIC IGF DEFICIENCY.

A patient with:

ACROMEGALY

needs:

LESS IGF-1 SIGNALING.

Same molecule.

Different:

THERAPEUTIC DIRECTION.

SEVEN QUESTIONS TO ASK BEFORE TARGETING IGF-1

1. WHY IS IGF-1 LOW OR HIGH?

GH deficiency?

GH resistance?

nutrition?

liver?

puberty?

age?

acromegaly?

2. WHERE IN THE AXIS IS THE FAILURE?

hypothalamus?

pituitary?

GH receptor?

liver?

IGF1R?

3. IS SERUM IGF-1 ACTUALLY REPRESENTING THE PHYSIOLOGY WE CARE ABOUT?

Remember:

local IGF signaling may differ.

4. WHAT ARE THE BINDING PROTEINS DOING?

IGFBP-3?

IGFBP-1?

ALS?

proteolysis?

5. WHAT IS THE NUTRITIONAL STATE?

Because:

GROWTH SIGNALING REQUIRES SUBSTRATE.

6. WHAT OUTCOME WILL BE MEASURED?

linear growth?
bone?
muscle?
glucose?
disease control?

7. WHAT WOULD DEFINE SUCCESS?

Not:

“THE IGF-1 NUMBER WENT UP.”

But:

THE SPECIFIC GROWTH OR METABOLIC DEFECT IMPROVED - HEIGHT VELOCITY, BODY COMPOSITION, TISSUE FUNCTION, OR DISEASE CONTROL MOVED IN THE DESIRED DIRECTION - WHILE GLUCOSE, GROWTH RATE, SOFT-TISSUE EFFECTS, ORTHOPEDIC STATUS, AND WHOLE-PATIENT PHYSIOLOGY REMAINED APPROPRIATE.

KEY TAKEAWAYS

IGF-1 is a 70-amino-acid growth factor produced by the liver and many local tissues.

It is a major downstream mediator of growth-hormone physiology but is not simply “active GH.”

GH and IGF-1 are separate signals with distinct receptors and different metabolic effects.

GH activates the GH receptor.

IGF-1 activates IGF1R.

IGF1R is a receptor tyrosine kinase that signals through major pathways including PI3K-AKT and RAS-MAPK.

These pathways regulate protein synthesis, survival, proliferation, differentiation, and metabolism.

IGF-1 is therefore central to linear growth, bone biology, muscle anabolic signaling, and tissue development.

But serum IGF-1 is only one layer of the system.

Many tissues produce IGF-1 locally, and most circulating IGF-1 is bound to IGF-binding proteins rather than freely available.

IGFBP-3, IGFBP-5, and the acid-labile subunit ALS form a large circulating reservoir that greatly extends IGF half-life.

This means binding proteins do not simply turn IGF-1 off.

They transport it, preserve it, restrain it, and help determine when it becomes available to receptors.

Local proteases such as PAPP-A and PAPP-A2 can then alter IGF availability by cleaving selected IGFBPs.

The IGF system is therefore a regulated delivery network, not simply a circulating hormone concentration.

IGF-1 is also highly nutrient sensitive.

During fasting or malnutrition, GH can rise while IGF-1 falls.

That is not contradictory.

GH helps mobilize fuel during fasting.

Low nutrient availability tells the liver not to fully activate the growth program.

This is why IGF-1 can be understood partly as a nutrient-permission signal.

Direct recombinant IGF-1 therapy has a legitimate but highly specific clinical role.

Mecasermin is FDA approved for selected children with severe primary IGF-1 deficiency or GH-gene deletion with neutralizing GH antibodies.

It is not a general substitute for growth hormone.

That distinction is one of the strongest examples of axis localization in endocrine medicine.

If GH is missing, address GH.

If GH is present but the body cannot generate adequate IGF-1 because of severe primary IGF deficiency, downstream IGF-1 replacement can make mechanistic sense.

The major acute pharmacologic risk of direct IGF-1 therapy is hypoglycemia because IGF-1 has insulin-like glucose-lowering effects.

Additional risks such as lymphoid hypertrophy, intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression are also consistent with the biology of accelerated growth.

Again:

THE THERAPEUTIC EFFECT AND THE ADVERSE EFFECT COME FROM THE SAME PATHWAY.

IGF-1 is also one of the clearest examples of why “anabolic” does not automatically mean “better.”

Too little signaling causes growth failure.

Too much signaling can create pathological growth.

The target is not maximum IGF-1.

The target is context-appropriate IGF signaling.

THE BOTTOM LINE

IGF-1 is often introduced as:

“THE HORMONE THAT GROWTH HORMONE MAKES.”

That is technically useful.

But it misses the deeper biology.

GH is a:

SIGNAL.

IGF-1 is another:

SIGNAL.

The two cooperate.

But they are not identical.

GH rises during fasting.

Yet IGF-1 may fall.

Why?

Because:

THE BODY NEEDS FUEL MOBILIZATION WITHOUT ENTERING A FULL GROWTH STATE.

Then nutrients return.

Insulin rises.

The liver becomes more responsive.

IGF-1 rises.

Now:

GROWTH BECOMES PERMITTED.

That alone tells us IGF-1 is doing more than:

FOLLOWING GH.

It is integrating:

GH + NUTRITION + INSULIN + LIVER CAPACITY.

Then the body takes another step.

It does not allow most IGF-1 to float freely.

It binds it.

IGFBP-3.

ALS.

Large ternary complex.

Why?

Because:

a powerful insulin-like growth factor needs:

CONTROL.

The binding system makes IGF-1:

- last longer
- travel safely
- remain less immediately active

Then local tissues can release more of the signal when:

THE LOCAL ENVIRONMENT NEEDS IT.

So:

IGF biology is not:

HOW MUCH IGF-1 IS IN THE BLOOD?

It is:

HOW MUCH IS PRODUCED?

HOW MUCH IS BOUND?

HOW MUCH IS AVAILABLE?

WHICH RECEPTOR IS PRESENT?

WHAT NUTRIENTS EXIST?

WHAT TISSUE IS RECEIVING THE SIGNAL?

WHAT OTHER GROWTH PATHWAYS ARE ACTIVE?

And that is why direct IGF-1 therapy is so different from:

Tesamorelin.

Sermorelin.

CJC-1295.

Those manipulate:

THE UPSTREAM GH AXIS.

Mecasermin bypasses it and provides:

THE DOWNSTREAM GROWTH FACTOR DIRECTLY.

That can be exactly right when:

THE DOWNSTREAM SIGNAL IS WHAT IS MISSING.

And completely wrong when:

THE ACTUAL PROBLEM IS NUTRITION, LIVER FUNCTION, OR PITUITARY GH DEFICIENCY.

This is also why the next two IGF-related guides become so important.

IGF-1 LR3

and:

IGF-1 DES

are not simply:

“STRONGER IGF-1.”

Their modifications alter:

HOW THEY INTERACT WITH THE IGF-BINDING-PROTEIN SYSTEM.

And that changes the fundamental pharmacology.

Because:

BINDING-PROTEIN REGULATION IS PART OF IGF-1 PHYSIOLOGY.

- Remove that regulation

and you have not merely made:

MORE IGF-1.

You have created:

A DIFFERENT SIGNALING SYSTEM.

So the Praxis question becomes:

“WHY is the IGF-1 signal abnormal, is the problem insufficient GH, GH resistance, poor hepatic IGF production, inadequate nutrition, altered IGF-binding-protein biology, impaired IGF1R signaling, or excessive pathway activity, and would changing IGF-1 itself correct the limiting physiological node without creating inappropriate glucose lowering, uncontrolled tissue growth, or growth-factor exposure in tissues that were never the therapeutic target?”

That is the difference between:

CALLING IGF-1 AN ANABOLIC PEPTIDE

and:

UNDERSTANDING THE GH-IGF-IGFBP GROWTH-SIGNALING SYSTEM.

FINAL RECALL

LOCALIZE Find the failed axis node	PERMIT Check nutrition, liver, insulin, and IGFBPs	VERIFY Measure function, glucose, growth rate, and tissue effects
--	--	---

STOP MEMORIZING PEPTIDES. START UNDERSTANDING THE SYSTEM.

Praxis Peptide Institute provides educational information and is not a substitute for individualized medical diagnosis or treatment. IGF-1 is an endogenous 70-amino-acid growth factor regulated by GH, nutrition, insulin, liver function, IGF-binding proteins, and tissue-specific production. Direct recombinant IGF-1 therapy has a highly specific established role in selected pediatric severe primary IGF-1-deficiency states and should not be treated as interchangeable with growth hormone, GHRH analogs, or modified IGF analogs. Clinical interpretation should distinguish total serum IGF-1 from local and bioavailable IGF activity and should localize any abnormality within the broader hypothalamic-pituitary-GH-IGF-IGFBP system before assigning therapeutic meaning.