PRAXIS
PEPTIDE INSTITUTE

# IGF-1 LR3

## ADVANCED MECHANISM AND EVIDENCE GUIDE

BINDING-PROTEIN-RESISTANT LONG R3 IGF-1 RECEPTOR AGONIST
83 amino acids • Arg3 substitution • 13-aa extension • reduced IGFBP binding • IGF1R • PI3K-AKT-mTOR • MAPK

MEMORY KEY: LONG MEANS THE N-TERMINAL EXTENSION; R3 MEANS ARGININE AT POSITION 3. TOGETHER THEY WEAKEN THE IGFBP BRAKE.

Educational monograph • Strong molecular and cell-culture evidence • Meaningful preclinical biology • Very limited direct human outcomes

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

| EVIDENCE CODE | | CORE DISCIPLINE |
|---|---|---|
| | CELL = mechanistic<br>ANIMAL = organism-level preclinical<br>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 Igf-1 Lr3; the remaining pages add mechanism, evidence, context, and nuance.

| | |
|---|---|
| 01 | IDENTITY<br>A synthetic 83-amino-acid IGF-1 analog with a 13-amino-acid N-terminal extension and Arg at position 3. |
| 02 | DESIGN<br>The Long and R3 changes sharply reduce IGF-binding-protein affinity while retaining IGF1R activity. |
| 03 | ACCESS<br>Apparent potency largely reflects less IGFBP sequestration and greater receptor access - not a new receptor. |
| 04 | SIGNAL<br>Activates IGF1R pathways including IRS-PI3K-AKT-mTOR and SHC-RAS-RAF-MEK-ERK. |
| 05 | SYSTEM<br>Direct downstream signaling bypasses GH-axis control and can reorganize endogenous GH, IGF-1, and IGFBP markers. |
| 06 | SELECTIVITY<br>A systemic growth factor cannot distinguish intended muscle from gut, heart, kidney, spleen, or unwanted cells. |
| 07 | EVIDENCE<br>Its laboratory growth-factor use is established; human hypertrophy, recovery, performance, and longevity outcomes are not. |
| 08 | PRAXIS QUESTION<br>Why weaken IGFBP control, which tissue is targeted, what else receives the signal, and did function improve safely? |

**ONE-SENTENCE MEMORY**
**LONG MEANS THE N-TERMINAL EXTENSION; R3 MEANS ARGININE AT POSITION 3. TOGETHER THEY WEAKEN THE IGFBP BRAKE.**

# UNDERSTAND THE PEPTIDE

IGF-1 LR3 - Long R3 IGF-1 - is a synthetic 83-amino-acid analog of human insulin-like growth factor-1 engineered to interact far less strongly with IGF-binding proteins while retaining activity at the IGF-1 receptor.

Native human IGF-1 contains:

**70 AMINO ACIDS.**

IGF-1 LR3 contains:

**83 AMINO ACIDS.**

**Why?**

Because researchers made two major modifications.

## MODIFICATION 1

The glutamic acid at position 3 of the native IGF-1 portion was replaced by:

**ARGININE.**

Hence:

**R3 - ARG³.**

## MODIFICATION 2

A:

**13-AMINO-ACID N-TERMINAL EXTENSION**

was added.

Together:

• 70-aa IGF-1

**13-aa extension** → **83-AA LONG R3 IGF-1.**

The purpose of these changes was not primarily to discover a new receptor.

IGF-1 LR3 still acts through:

**IGF1R.**

The major objective was to change:

**HOW THE LIGAND INTERACTS WITH THE IGF-BINDING-PROTEIN SYSTEM.**

Experimental literature describes Long R3 IGF-1 as maintaining IGF1R activity while having dramatically reduced affinity for IGFBPs compared with native IGF-1.

That is the central concept.

The best description is:

IGF-1 LR3 IS AN IGF-1 ANALOG ENGINEERED TO ESCAPE MUCH OF THE NORMAL IGF-BINDING-PROTEIN RESTRAINT THAT REGULATES NATIVE IGF-1.

That one sentence explains almost everything that follows.

# THE MOST IMPORTANT DIFFERENCE FROM NATIVE IGF-1

Native IGF-1 does not simply circulate:

**FREE.**

Most circulating IGF-1 is controlled by:

**IGFBP-1**

**IGFBP-2**

**IGFBP-3**

**IGFBP-4**

**IGFBP-5**

**IGFBP-6**

and especially the large circulating:

**IGF-1 + IGFBP-3 + ALS**

ternary complex.

Those proteins:

- transport IGF-1
- extend its circulating residence
- regulate tissue delivery
- protect it
- reduce immediate receptor access

So native IGF physiology is partly:

**A BINDING-PROTEIN-GATED SYSTEM.**

IGF-1 LR3 was engineered to:

**WEAKEN THAT GATE.**

**Again:**

**THIS IS NOT JUST "STRONGER IGF-1."**

It is:

**IGF-1 WITH ALTERED REGULATORY PHYSIOLOGY.**

# THE CENTRAL DESIGN

**Native IGF-1** → **high-affinity interaction with IGFBPs** → **storage / transport / restraint** → **controlled receptor availability.**

| | | | | | | |
|---|---|---|---|---|---|---|
| **IGF-1 LR3** | → | **markedly reduced IGFBP binding** | → | **less sequestration by IGFBPs** | → | **greater access to:** |

**IGF1R**

in many experimental settings.

**Again:**

**THE MODIFICATION CHANGES BIOAVAILABILITY MORE THAN RECEPTOR IDENTITY.**

# WHY THE FIRST FEW AMINO ACIDS MATTER SO MUCH

The N-terminal region of IGF-1 contributes substantially to:

**IGFBP INTERACTION.**

Researchers found that:

- substitutions
- deletions
- extensions

around the N-terminus could dramatically change:

**BINDING-PROTEIN AFFINITY.**

Long R3 IGF-1 incorporates both:

**AN ARG³ SUBSTITUTION**

and:

**A 13-AA EXTENSION.**

Experimental studies describe the Arg3 change and N-terminal modification as dramatically reducing the analog's ability to bind IGFBPs while retaining biological activity at the type-1 IGF receptor.

**Again:**

**SMALL SEQUENCE MODIFICATIONS CAN RADICALLY ALTER PROTEIN-BINDING PHARMACOLOGY.**

# THE STRUCTURE

Native IGF-1:

| | | |
|---|---|---|
| **70 aa** | → | **position 3:** |

glutamic acid.

**IGF-1 LR3:**

| | | |
|---|---|---|
| **83 aa** | → | **13-aa N-terminal extension** |

Arg replacing Glu at position 3 of the IGF-1 domain.

Commercial biochemical references describe this exact architecture and note the dramatically reduced interaction with IGF-binding proteins.

**Again:**

**THE NAME TELLS YOU THE DESIGN.**

LONG = N-terminal extension.

R3 = arginine substitution at position 3.

# WHAT THE “LONG” PART DOES

The 13-amino-acid extension is not simply:

**EXTRA DECORATION.**

It changes how the N-terminal IGF region interacts with:

IGFBPs.

Combined with the Arg3 substitution:

the analog becomes much less effectively sequestered by the endogenous IGFBP system.

**Again:**

**THE EXTENSION CHANGES ACCESS.**

# WHAT THE “R3” PART DOES

R3 refers to:

**ARGININE AT POSITION 3.**

Native IGF-1 has:

**GLUTAMIC ACID**

at that site.

Replacing a:

• negatively charged glutamate

with:

• positively charged arginine

alters local ligand chemistry.

That helps reduce:

**IGFBP AFFINITY.**

**Again:**

**ONE CHARGE REVERSAL CAN CHANGE PROTEIN-PROTEIN INTERACTION DRAMATICALLY.**

# IGF-1 LR3 STILL ACTS THROUGH IGF1R

This is crucial.

The molecule was not engineered to create:

**A NEW GROWTH-FACTOR RECEPTOR.**

Its principal receptor remains:

**IGF1R - THE TYPE-1 IGF RECEPTOR.**

**Therefore:**

**IGF-1 LR3**

**IGF1R → receptor tyrosine kinase activation → IRS / SHC-related signaling → PI3K → AKT**

and:

**RAS → RAF → MEK → ERK**

- growth
- protein synthesis
- survival
- metabolism

proliferation.

**Again:**

**RECEPTOR SAME. REGULATORY ACCESS DIFFERENT.**

# THE IGF1R PATHWAY

**IGF-1 LR3 → IGF1R → tyrosine au tophosphor ylation → IRS proteins → PI3K → AKT → mTOR-relat ed signaling → PROTEIN SYNTHESIS / SURVIVAL / METABOLIC SIGNALING**

and:

**IGF1R**

**SHC / RAS → RAF → MEK → ERK → PROLIFERATION / DIFFERENTIATION / GROWTH.**

**Again:**

this is the same broad intracellular network discussed in:

**NATIVE IGF-1.**

The key difference is:

HOW EASILY THE ANALOG REACHES THE RECEPTOR IN THE PRESENCE OF IGFBPs.

# IGF-1 LR3 VS NATIVE IGF-1

This comparison is essential.

### NATIVE IGF-1

70 aa.

Strongly regulated by:

IGFBPs.

Much circulating IGF exists in:

**BOUND COMPLEXES.**

Receptor access is:

highly regulated.

### IGF-1 LR3

83 aa.

Arg3 substitution.

13-aa N-terminal extension.

Markedly reduced IGFBP affinity.

IGF1R activity retained.

**Again:**

**NATIVE IGF-1 = REGULATED GROWTH FACTOR.**

**LR3 = BINDING-PROTEIN-RESISTANT GROWTH-FACTOR ANALOG.**

# THE MOST IMPORTANT PRAXIS DISTINCTION

Native IGF physiology says:

**MAKE IGF-1**

**bind most of it** → **transport it** → **restrain it** → **release it where appropriate.**

LR3 changes that equation.

It asks:

**WHAT HAPPENS IF THE GROWTH FACTOR IS MUCH HARDER FOR THE BINDING-PROTEIN SYSTEM TO CONTROL?**

That is a very different biological experiment.

• IGFBPs ARE NOT JUST “BLOCKERS”

This matters especially here.

If someone says:

• LR3 binds IGFBPs less

**therefore:**

**BETTER.**

That is too simplistic.

Remember from the IGF-1 guide:

IGFBPs do several things.

They can:

- sequester IGF
- transport it
- prevent indiscriminate receptor activation
- prolong half-life
- regulate tissue delivery

create local IGF reservoirs.

**So:**

lower IGFBP binding can increase:

**IMMEDIATE BIOAVAILABILITY**

but may reduce:

**PHYSIOLOGICAL COMPARTMENTALIZATION.**

**Again:**

**ESCAPING A REGULATORY SYSTEM IS NOT AUTOMATICALLY AN IMPROVEMENT.**

# THE RESERVOIR VS ACCESS TRADEOFF

| | | | | |
|---|---|---|---|---|
| **Native IGF-1** | → | **binds IGFBPs strongly** | → | **less immediately available** |

**but:**

better transported / buffered / stored.

| | | | | |
|---|---|---|---|---|
| **LR3** | → | **weak IGFBP binding** | → | **more receptor-accessible** |

**but:**

less participation in:

**THE NORMAL IGF RESERVOIR SYSTEM.**

**Again:**

**BIOAVAILABILITY AND PHYSIOLOGICAL CONTROL ARE NOT THE SAME THING.**

# IGF-1 LR3 IS OFTEN DESCRIBED AS “MORE POTENT”

That statement needs nuance.

In many biological systems:

LR3 can appear much more potent than native IGF-1.

**Why?**

Because:

| | | |
|---|---|---|
| **native IGF-1** | → | **gets bound by IGFBPs.** |
| **LR3** | → | **largely escapes them.** |

So in a culture system containing IGFBPs:

more LR3 remains available to:

**IGF1R.**

This can make LR3 appear:

**FAR MORE BIOLOGICALLY ACTIVE.**

However:

that does not necessarily mean LR3 is intrinsically a dramatically stronger:

**IGF1R AGONIST MOLECULE-FOR-MOLECULE.**

One study comparing IGF1R activation found Long R3 IGF-I was not intrinsically more potent than recombinant human IGF-I at the receptor under equimolar conditions, despite its potential for greater in-vivo or culture-system activity because of reduced IGFBP binding.

**Again:**

**APPARENT POTENCY CAN COME FROM ESCAPING BINDING PROTEINS - NOT FROM A SUPERIOR RECEPTOR.**

# THIS IS A HUGE CONCEPT

Imagine:

Ligand A:

• excellent receptor agonist

**but:**

90% bound.

Ligand B:

• similar receptor agonist

**but:**

only minimally bound.

In biological fluid:

Ligand B may produce:

much more effect.

**Why?**

Not necessarily because:

**THE RECEPTOR LIKES IT MORE.**

But because:

**MORE OF IT CAN REACH THE RECEPTOR.**

**Again:**

**PHARMACOKINETIC / DISTRIBUTIONAL POTENCY ≠ RECEPTOR-INTRINSIC POTENCY.**

## IGF-1 LR3 WAS DEVELOPED LARGELY AS A RESEARCH / CELL-CULTURE TOOL

This is frequently overlooked.

Long R3 IGF-I became especially valuable in:

**CELL CULTURE.**

**Why?**

Cells in culture can secrete:

IGFBPs.

Those binding proteins can neutralize or complicate native IGF-1 supplementation.

**LR3:** → **binds those proteins much less strongly** → **remains available to cells** → **supports:**

- proliferation
- viability
- protein production

more consistently.

Commercial life-science suppliers still market Long R3 IGF-I specifically as a growth-factor supplement for serum-free or low-serum cell-culture systems.

**Again:**

**ONE OF LR3'S CLEAREST ESTABLISHED USES IS AS A LABORATORY GROWTH FACTOR.**

That does not automatically translate into:

**A HUMAN THERAPEUTIC DRUG.**

# THE CELL-CULTURE LOGIC

**Cell culture → cells produce IGFBPs → native IGF-1 becomes sequestered → growth response reduced.**

Add:

**LR3**

**IGFBPs bind poorly → IGF1R remains accessible → cell proliferation / viability improves.**

**Again:**

**THE ANALOG WAS DESIGNED TO SOLVE A CELL-CULTURE REGULATION PROBLEM.**

# CELL CULTURE SUCCESS ≠ HUMAN THERAPEUTIC SUCCESS

This distinction cannot be overstated.

A bioreactor wants:

**MAXIMUM CONSISTENT CELL GROWTH.**

A human body does not.

The human body wants:

**CONTROLLED TISSUE-SPECIFIC GROWTH.**

Those are different objectives.

**Again:**

**WHAT IS GOOD FOR CHO CELL PRODUCTION IS NOT AUTOMATICALLY GOOD FOR HUMAN SYSTEMIC PHYSIOLOGY.**

# THE BIOREACTOR VS HUMAN PRINCIPLE

Bioreactor:

**more viable cells → better protein manufacturing.**

Human:

**indiscriminate growth-factor exposure → potential effects on:**

- muscle
- kidney
- gut
- liver
- spleen
- tumor tissue

glucose.

**Again:**

**THE TARGET FUNCTION DEFINES WHETHER POTENCY IS GOOD.**

# IGF-1 LR3 AND MUSCLE

This is why LR3 became so famous outside laboratories.

**IGF1R → PI3K → AKT → mTOR → protein synthesis.**

Also:

IGF signaling can influence:

• satellite cells

• myoblast proliferation

• differentiation

muscle growth.

**So:**

**LR3**

• with increased biological availability

appears mechanistically attractive for:

**MUSCLE GROWTH.**

Cell-culture studies do demonstrate that Long R3 IGF-I can stimulate myogenic-cell proliferation and differentiation-related biology.

**Again:**

**THE MUSCLE MECHANISM IS REAL.**

**But:**

**THE HUMAN PERFORMANCE CLAIM IS A DIFFERENT EVIDENCE LEVEL.**

# MYOBLAST GROWTH ≠ HUMAN HYPERTROPHY

**L6 myogenic cells → LR3 → proliferation / signaling.**

That proves:

**CELLULAR RESPONSIVENESS.**

It does not prove:

**healthy adult human → LR3 → safe, selective skeletal-muscle hypertrophy → strength ↑ → performance ↑.**

**Again:**

**CELL CULTURE IS THE FIRST RUNG, NOT THE LAST.**

## IGF-1 LR3 AND SATELLITE CELLS

IGF signaling contributes to:

• satellite-cell activation

• myoblast proliferation

differentiation.

This is why the molecule is frequently discussed around:

**HYPERTROPHY.**

But satellite-cell biology depends on:

| | |
|---|---|
| • injury / loading | • local inflammatory signals |
| • mechanical tension | • extracellular matrix |

nutrient availability.

**Again:**

**GROWTH FACTOR ≠ COMPLETE MUSCLE-ADAPTATION PROGRAM.**

## THE MUSCLE-BUILDING SYSTEM

| | | |
|---|---|---|
| **Mechanical tension** | → | **mechanotransduction** |
| **amino acids** | → | **mTOR substrate availability** |
| **androgens / insulin / IGF signaling** | → | **adaptation.** |

**So:**

LR3 can potentially amplify:

**ONE POWERFUL ANABOLIC SIGNAL.**

It cannot substitute for:

**THE REST OF THE SYSTEM.**

## LOCAL IGF-1 VS SYSTEMIC LR3

This distinction is extremely important.

Exercise induces:

**LOCAL IGF-RELATED SIGNALING**

within muscle.

That is geographically constrained.

Systemic LR3:

potentially exposes:

**MANY IGF1R-CONTAINING TISSUES.**

**Again:**

**LOCAL ANABOLISM ≠ SYSTEMIC GROWTH-FACTOR EXPOSURE.**

This is one of the biggest conceptual differences.

## THE TARGETING PROBLEM

Desired:

skeletal muscle.

Drug:

systemic IGF1R agonist.

But IGF1R also exists in:

- bone
- gut
- nervous tissue
- kidney
- vascular tissue
- many tumors

many other organs.

**Again:**

**SYSTEMIC RECEPTOR AGONISM DOES NOT KNOW WHICH TISSUE YOU WANTED.**

## ANIMAL STUDIES MAKE THIS VERY CLEAR

In guinea pigs, seven-day Long R3 IGF-I infusion increased the relative weights of multiple organs including:

- adrenals
- kidneys
- gut
- spleen

without significantly increasing overall body growth.

That is an exceptionally important finding.

**Why?**

Because it illustrates:

SYSTEMIC GROWTH-FACTOR SIGNALING CAN CREATE ORGAN-SPECIFIC GROWTH WITHOUT PRODUCING THE SIMPLE BODY-COMPOSITION OUTCOME PEOPLE EXPECT.

**Again:**

**MORE GROWTH SIGNAL DOES NOT MEAN “MORE MUSCLE.”**

# THE ORGAN-GROWTH PRINCIPLE

**Systemic LR3** → **IGF1R across body** → **some tissues respond strongly.**

Possible result:

• organ enlargement

without:

desired total-body hypertrophy.

**Again:**

**ANABOLIC SIGNALING IS NOT MUSCLE SELECTIVE.**

**ANOTHER ANIMAL STUDY MAKES THE STORY EVEN MORE COMPLEX**

In pigs, Long R3 IGF-I infusion actually:

- reduced average daily weight gain
- reduced circulating IGFBP-3
- reduced insulin
- reduced food intake
- reduced endogenous IGF-I
- reduced mean GH

reduced GH pulse area.

That finding is important because it directly challenges the simplistic idea:

**LR3**

**more IGF signal** → **more growth.**

No.

The endocrine system responded with:

**FEEDBACK + SYSTEMIC ADAPTATION.**

**Again:**

**EXOGENOUS GROWTH SIGNAL CAN SUPPRESS ENDOGENOUS GROWTH AXES.**

# THE FEEDBACK MODEL

**LR3** → **IGF1R signaling ↑** → **hypothalamic / pituitary feedback** → **GH secretion ↓** → **endogenous IGF-1 production ↓**

potential changes in:

• IGFBPs

• insulin

food intake.

**Again:**

**THE BODY PUSHES BACK.**

**THIS IS WHY IGF-1 LR3 CANNOT BE UNDERSTOOD AS “ADDED IGF”**

If you add LR3:

you may not simply get:

• native IGF system

extra IGF activity.

You may get:

- LR3 activity
- suppressed endogenous IGF-1
- changed insulin
- suppressed GH
- altered IGFBPs

changed food intake.

**Again:**

**THE SYSTEM REORGANIZES AROUND THE SIGNAL.**

This is quintessential Praxis physiology.

# IGF-1 LR3 AND GH

Unlike:

**CJC-1295**

• Sermorelin

**GHRP-2**

**GHRP-6**

• Ipamorelin

LR3 does not need to stimulate:

**THE PITUITARY FIRST.**

It acts:

**DOWNSTREAM.**

**So:**

**LR3**

**IGF1R**

directly.

That means:

it bypasses:

**GHRH**

### GHSR

• pituitary GH secretion

much of hepatic IGF generation.

**Again:**

**LR3 IS A DOWNSTREAM GROWTH-FACTOR INTERVENTION.**

## THE BYPASS PRINCIPLE

**GHRH analog → pituitary → GH → liver → IGF-1.**

**LR3: → IGF1R.**

Much shorter path.

**But:**

the shorter path means:

**LESS UPSTREAM CONTROL.**

**Again:**

**BYPASSING A REGULATORY AXIS INCREASES DIRECTNESS AND REDUCES PHYSIOLOGICAL GOVERNANCE.**

## THIS IS THE SAME LESSON AS MECASERMIN - BUT MORE EXTREME

Mecasermin:

**recombinant human IGF-1. → still native IGF-1 sequence. → still interacts with:**

IGFBPs.

### LR3:

**modified IGF-1 → far less IGFBP interaction.**

**So:**

• direct IGF-1 therapy

already bypasses:

the GH axis.

LR3 potentially bypasses:

**ANOTHER REGULATORY LAYER AS WELL.**

**Again:**

**GH CONTROL BYPASSED**

### IGFBP CONTROL REDUCED.

That is a fundamentally more synthetic signaling environment.

## IGF-1 LR3 VS MECASERMIN

### MECASERMIN

recombinant human IGF-1.

70 aa.

Native sequence.

Human therapeutic development.

Established use in:

**SEVERE PRIMARY IGF-1 DEFICIENCY.**

Strong interaction with:

IGFBPs.

### IGF-1 LR3

83 aa.

Arg3 substitution.

13-aa N-terminal extension.

markedly reduced IGFBP binding.

Research / cell-culture analog.

No comparable established therapeutic human evidence base.

**Again:**

**MECASERMIN EVIDENCE ≠ LR3 EVIDENCE.**

This distinction is essential.

## DO NOT BORROW MECASERMIN DATA

Wrong logic:

Mecasermin treats severe IGF-1 deficiency.

LR3 activates IGF1R.

**Therefore:**

LR3 is a better treatment.

No.

Because:

mecasermin's clinical evidence belongs to:

**MECASERMIN.**

LR3 alters:

- binding-protein interaction
- distribution
- exposure
- feedback

possibly tissue selectivity.

**Again:**

**MODIFIED ANALOG ≠ CLINICALLY VALIDATED UPGRADE.**

# IGF-1 LR3 AND GLUCOSE

IGF1R signaling has:

**INSULIN-LIKE METABOLIC EFFECTS.**

Native IGF-1 can:

• enhance glucose uptake

• suppress hepatic glucose production

lower blood glucose.

**Therefore:**

a highly bioavailable IGF analog raises obvious questions about:

**HYPOGLYCEMIA.**

Direct high-quality LR3-specific human safety data are extremely limited.

But mechanistically:

**GLUCOSE LOWERING IS A PLAUSIBLE ON-PATHWAY CONCERN.**

**Again:**

**THE NAME “INSULIN-LIKE” STILL MATTERS.**

# THE GLUCOSE MODEL

**LR3** → **IGF1R** → **AKT signaling** → **glucose uptake ↑**

**hepatic glucose production may ↓** → **blood glucose may fall.**

Meanwhile:

**endogenous GH may be suppressed** → **less GH-mediated glucose mobilization.**

**Again:**

**MULTIPLE SIGNALS COULD PUSH GLUCOSE DOWNWARD.**

# IGF1R AND INSULIN-RECEPTOR CROSS-TALK

IGF1R and the insulin receptor are:

**CLOSELY RELATED RECEPTOR TYROSINE KINASES.**

They can form:

**HYBRID RECEPTORS.**

At sufficiently high ligand concentrations:

cross-family receptor signaling may become relevant.

**Again:**

**PHARMACOLOGICAL CONCENTRATION CAN CREATE RECEPTOR BEHAVIOR DIFFERENT FROM PHYSIOLOGICAL CONCENTRATION.**

That is another reason:

dose-response and exposure matter.

# IGF-1 LR3 AND PROLIFERATION

IGF1R activates:

**RAS-MAPK**

and:

**PI3K-AKT.**

These support:

• survival

• proliferation

anti-apoptotic signaling.

That is normal physiology.

But it means systemic LR3 cannot simply be treated as:

**A MUSCLE SIGNAL.**

It is:

**A GROWTH / SURVIVAL SIGNAL.**

**Again:**

**THE SAME PATHWAY THAT HELPS A MYOBLAST SURVIVE MAY ALSO HELP AN UNWANTED CELL SURVIVE.**

# IGF-1 LR3 AND CANCER CONTEXT

This needs careful wording.

IGF-1 LR3 does not:

**“CAUSE CANCER”**

by definition.

But IGF1R signaling is implicated in:

- proliferation
- survival
- resistance to apoptosis
- tumor biology

in numerous malignancies.

A particularly instructive animal cachexia study found that Long R3 IGF-I limited muscle loss but was accompanied by:

**ACCELERATED TUMOR GROWTH.**

That is exactly the kind of result that deserves attention.

**Why?**

Because it demonstrates:

**THE GROWTH SIGNAL DOES NOT KNOW WHICH TISSUE IS THE THERAPEUTIC TARGET.**

# THE TUMOR-MUSCLE TRADEOFF

**Cachectic animal** → **LR3** → **muscle preservation improved.**

**But:**

**tumor also receives growth/survival signaling** → **tumor growth accelerated.**

**Again:**

**ANABOLIC BENEFIT IN ONE TISSUE CAN BECOME PROLIFERATIVE COST IN ANOTHER.**

This is a powerful Praxis lesson.

# GROWTH FACTOR ≠ MUSCLE FACTOR

This should be one of the boldest lines on the page.

**IGF-1 LR3 IS A GROWTH FACTOR ANALOG.**

Not:

**A MUSCLE-SELECTIVE FACTOR.**

That distinction changes:

- patient selection
- risk interpretation

• monitoring

evidence standards.

# IGF-1 LR3 AND GUT GROWTH

Animal studies have shown:

intestinal trophic effects.

For example, neonatal rats fed Long R3 IGF-I demonstrated increased intestinal villus height and cell counts compared with formula controls.

This demonstrates:

**REAL TISSUE-TROPHIC BIOLOGY.**

**But:**

it does not establish:

systemic LR3 as a human gut-repair therapy.

**Again:**

**ANIMAL INTESTINAL GROWTH ≠ HUMAN BARRIER REGENERATION PROOF.**

# IGF-1 LR3 AND ORGANOMEGALY

Given:

• IGF1R distribution

• animal organ-growth findings

• known biology of excessive GH/IGF signaling

the possibility of:

**UNDESIRED ORGAN GROWTH**

is mechanistically relevant.

**Again:**

the concern is not hypothetical because:

animal LR3 studies have directly demonstrated selective organ-weight increases.

That is different from claiming a specific human incidence.

The correct statement is:

THE PATHWAY AND PRECLINICAL DATA SUPPORT ORGAN-GROWTH CONCERN, WHILE PRECISE HUMAN LR3 RISK IS NOT WELL CHARACTERIZED.

# IGF-1 LR3 AND HEART

IGF signaling can support:

• cardiomyocyte growth

• survival

hypertrophic signaling.

That can be adaptive in some contexts.

But chronic excessive growth-factor signaling can contribute to:

**CARDIAC REMODELING.**

**Again:**

**TROPHIC EFFECT ≠ ALWAYS BENEFICIAL EFFECT.**

Dose + duration + tissue context matter.

## IGF-1 LR3 AND KIDNEY

IGF signaling can influence:

• renal growth

• renal blood flow

tubular physiology.

Animal LR3 studies showing increased kidney relative weight further reinforce:

**THE SYSTEMIC NATURE OF THE SIGNAL.**

**Again:**

**THE KIDNEY RECEIVES THE DRUG TOO.**

## IGF-1 LR3 AND SPLEEN / IMMUNE TISSUE

In the same guinea-pig study:

spleen weight increased.

That does not establish:

**IMMUNE BENEFIT.**

It establishes:

**TROPHIC RESPONSIVENESS.**

**Again:**

**BIGGER ORGAN ≠ BETTER ORGAN.**

## IGF-1 LR3 AND “LOCAL INJECTION” CLAIMS

One recurring idea is that administering LR3 near a muscle will cause:

**SITE-SPECIFIC GROWTH.**

That claim is not well established.

Once a peptide reaches:

**SYSTEMIC CIRCULATION,**

its receptor exposure is not automatically limited to:

the nearby muscle.

Local pharmacokinetics depend on:

- absorption
- blood flow
- tissue diffusion
- receptor density

clearance.

**Again:**

**INJECTION LOCATION ≠ GUARANTEED TISSUE SELECTIVITY.**

This is a major distinction.

# THE LOCALITY ERROR

**Inject near biceps.** → **does not automatically mean:**

biceps receives all the peptide.

**Drug enters interstitial fluid** → **circulation** → **other tissues.**

**Again:**

**GEOGRAPHIC INJECTION SITE ≠ MOLECULAR TARGETING TECHNOLOGY.**

True tissue targeting requires:

- delivery vehicles
- local depot
- receptor targeting
- gene-expression strategy

tissue-specific pharmacology.

Not simply:

**“PUT IT NEAR THE MUSCLE.”**

# IGF-1 LR3 AND PERFORMANCE

The performance logic is obvious.

**LR3** → **IGF1R** → **anabolism.**

But direct high-quality controlled human trials demonstrating:

- increased strength
- improved endurance
- improved sprint performance
- enhanced competition outcomes

are lacking.

**Again:**

**ANABOLIC PATHWAY ≠ ATHLETIC-PERFORMANCE EVIDENCE.**

# MASS ≠ PERFORMANCE

Even if muscle mass increased:

performance also depends on:

- motor control
- cardiovascular capacity
- tendon stiffness
- technique

neuromuscular coordination.

**Again:**

**MORE TISSUE ≠ BETTER ATHLETE AUTOMATICALLY.**

# IGF-1 LR3 AND RECOVERY

**Again:**

the pathway makes recovery claims plausible.

IGF signaling affects:

- protein synthesis
- survival
- connective tissue

cellular repair.

But direct LR3 human evidence for:

- injury recovery
- ligament repair
- tendon repair
- postexercise recovery

is extremely limited.

**Again:**

**THE PATHWAY IS STRONGER THAN THE CLAIM.**

# IGF-1 LR3 AND CARTILAGE

IGF1R signaling can stimulate:

- chondrocytes
- proteoglycan synthesis

extracellular matrix.

**But:**

systemic LR3 is not established as:

**AN OSTEOARTHRITIS-REGENERATIVE THERAPY.**

**Again:**

OA includes:

- mechanical loading
- subchondral bone
- inflammatory biology
- senescence

matrix degradation.

**ONE ANABOLIC SIGNAL ≠ JOINT REGENERATION.**

# IGF-1 LR3 AND NERVE BIOLOGY

IGF signaling has:

**NEUROTROPHIC PROPERTIES.**

That creates research interest in:

- nerve injury
- neurodegeneration

recovery.

**But:**

LR3-specific human neuroregenerative evidence is:

**NOT ESTABLISHED.**

**Again:**

**NEURONAL SURVIVAL PATHWAY ≠ CLINICAL NERVE REPAIR.**

# IGF-1 LR3 AND LONGEVITY

This is especially complicated.

High IGF signaling supports:

- growth
- protein synthesis

tissue maintenance.

But reduced IGF signaling has been linked to:

**LONGEVITY PHENOTYPES**

in many model organisms.

So describing LR3 as:

**ANTI-AGING**

is particularly simplistic.

**Again:**

**ANABOLISM AND LONGEVITY ARE NOT THE SAME BIOLOGICAL OBJECTIVE.**

**THE GROWTH-LONGEVITY TRADEOFF**

| | | |
|---|---|---|
| **IGF1R ↑** | → | **growth** |

• survival

protein synthesis.

**But:**

| | | |
|---|---|---|
| **lower insulin/IGF signaling in some organisms** | → | **stress resistance** |

• maintenance programs

longevity.

**Again:**

**THE SIGNAL BEST FOR RAPID GROWTH MAY NOT BE THE SIGNAL BEST FOR MAXIMUM LIFESPAN.**

# IGF-1 LR3 AND THE “HALF-LIFE” CLAIM

This is one of the most repeated claims online.

You will often see:

**20-30 HOURS**

or even:

**56-72 HOURS**

quoted as the human half-life of IGF-1 LR3.

The problem:

direct robust human pharmacokinetic evidence supporting these exact values is:

**VERY LIMITED.**

The molecule was engineered to reduce IGFBP interaction.

That absolutely changes its biological behavior.

**But:**

weak IGFBP binding does not automatically mean:

**LONGER CIRCULATING PLASMA HALF-LIFE.**

In fact:

binding proteins themselves often:

**PROLONG CIRCULATING IGF RESIDENCE.**

**Again:**

**LESS BINDING CAN MEAN GREATER BIOAVAILABILITY WITHOUT NECESSARILY MEANING LONGER BLOOD RESIDENCE.**

This distinction is crucial.

## THE BIG “LONG” MISUNDERSTANDING

The word:

**LONG**

in Long R3 IGF-I primarily refers to:

**THE 13-AMINO-ACID N-TERMINAL EXTENSION.**

It should not automatically be interpreted as:

**“LONGEST-CIRCULATING IGF.”**

**Again:**

**NAME ≠ HUMAN HALF-LIFE DATA.**

This is an important correction to common peptide marketing.

## IGFBP ESCAPE CAN ACTUALLY CHANGE CLEARANCE IN COMPLEX WAYS

Native IGF-1 bound to:

**IGFBP-3 + ALS**

**large ternary complex** → **remains in circulation longer.**

### LR3:

**binds weakly** → **does not enter the same reservoir efficiently** → **may move rapidly into:**

### TISSUES.

**So:**

the biological effect can be:

**STRONGER**

even if circulating blood persistence is not:

**LONGER.**

**Again:**

**TISSUE AVAILABILITY ≠ PLASMA HALF-LIFE.**

# THIS IS THE RIGHT WAY TO UNDERSTAND LR3

Not:

**“IT LASTS LONGER, SO IT IS STRONGER.”**

Better:

**“IT ESCAPES IGFBP SEQUESTRATION, WHICH CAN INCREASE EFFECTIVE RECEPTOR AVAILABILITY AND ALTER TISSUE DISTRIBUTION.”**

That is far more defensible.

**IGF-1 LR3 CAN ALTER ENDOGENOUS IGF MARKERS**

Remember the pig study.

LR3 infusion decreased:

• endogenous IGF-I

### IGFBP-3

### GH

insulin.

This creates a monitoring challenge.

Suppose:

serum native IGF-1 falls.

Does that mean:

overall IGF signaling fell?

Not necessarily.

LR3 itself may be providing:

**EXOGENOUS RECEPTOR DRIVE.**

**Again:**

**ENDOGENOUS BIOMARKER CAN FALL WHILE TOTAL PATHWAY SIGNALING RISES.**

That is a very important concept.

# THE BIOMARKER PARADOX

**LR3** → **IGF1R activity ↑** → **negative feedback** → **GH ↓** → **native IGF-1 ↓.**

**So:**

lab says:

IGF-1 down.

**But:**

receptor exposure may be:

**UP.**

**Again:**

**SERUM ENDOGENOUS IGF-1 ≠ TOTAL IGF1R SIGNAL UNDER ANALOG EXPOSURE.**

## THIS MAKES MONITORING HARDER

With native IGF-1 / GH-axis manipulation:

serum IGF-1 can sometimes function as:

a rough integrated marker.

With LR3:

assay cross-reactivity may vary.

Endogenous production may suppress.

Binding proteins may change.

**So:**

one total IGF-1 value may become:

**HARDER TO INTERPRET.**

**Again:**

**MODIFIED LIGAND CAN BREAK THE USUAL BIOMARKER MODEL.**

## ASSAY RECOGNITION MATTERS

Will a particular IGF-1 assay detect:

**LR3?**

That depends on:

• antibody epitopes

• assay design

sample preparation.

Some assays may:

• cross-react

• partially detect

• fail to detect

the analog.

**Again:**

**LAB NUMBER MAY NOT REPRESENT TRUE ANALOG EXPOSURE.**

This is a significant practical challenge.

# IGF-1 LR3 AND IGFBP-3 MEASUREMENT

If LR3 itself reduces or changes:

• IGFBP-3 physiology,

**then:**

IGFBP-3 becomes potentially informative.

**But:**

**again:**

changes could reflect:

• feedback

• GH suppression

direct systemic adaptation.

**Again:**

**THE WHOLE IGF NETWORK CAN MOVE.**

# IGF-1 LR3 VS IGF-1 DES

This is the perfect transition to the final guide.

Both analogs alter:

**NATIVE IGF-BINDING-PROTEIN INTERACTIONS.**

But they do so differently.

## IGF-1 LR3

• native IGF-1 domain

• Arg3 substitution

**13-aa N-terminal extension** → **83 aa** → **greatly reduced IGFBP binding.**

## IGF-1 DES

deletes:

**THE FIRST THREE AMINO ACIDS OF NATIVE IGF-1**

67 aa.

That deletion also dramatically reduces:

• IGFBP affinity

while maintaining strong IGF1R activity.

**Again:**

**LR3 ADDS + SUBSTITUTES.**

## DES REMOVES.

Different engineering strategies.

Same central objective:

**ALTER IGF REGULATION.**

## LR3 VS DES - THE BIG PHARMACOLOGY QUESTION

Which matters more:

receptor potency?

IGFBP escape?

tissue distribution?

clearance?

local retention?

That is exactly why:

these should remain separate guides.

**Again:**

**BOTH ARE “MODIFIED IGF-1” BUT THEY ARE NOT THE SAME ANALOG.**

# THE CORE MECHANISM MAP

## NATIVE IGF-1

| | | |
|---|---|---|
| **70 aa** | → | **normally binds strongly to:** |

## IGFBP-1 THROUGH IGFBP-6

especially:

| | | |
|---|---|---|
| **IGFBP-3 + ALS in circulation** | → | **transport / buffering / controlled availability.** |

**Then:**

engineering:

**ARG³ SUBSTITUTION**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **13-AA N-TERMINAL EXTENSION** | → | **IGF-1 LR3 - 83 aa** | → | **IGFBP affinity ↓↓↓** | → | **less sequestration** | → | **greater receptor accessibility in many experimental systems** | → | **IGF1R** | → | **receptor tyrosine kinase** | → | **PI3K → AKT → mTOR** |

- protein synthesis
- survival
- metabolic effects

## RAS → RAF → MEK → ERK

- growth
- proliferation

| | | |
|---|---|---|
| **differentiation** | → | **potential effects on:** |

| | |
|---|---|
| • muscle | • gut |
| • kidney | • spleen |
| • bone | • nervous tissue |
| • tumor tissue | |

glucose metabolism.

Meanwhile:

| | | | | |
|---|---|---|---|---|
| **strong IGF1R signaling** | → | **negative feedback** | → | **GH ↓** |

- endogenous IGF-1 ↓

IGFBP profile may change.

The core concept is:

IGF-1 LR3 DOES NOT CREATE A NEW IGF RECEPTOR - IT REMOVES MUCH OF THE BINDING-PROTEIN CONTROL THAT NORMALLY DETERMINES HOW NATIVE IGF-1 IS TRANSPORTED, BUFFERED, AND DELIVERED TO THAT RECEPTOR.

# WHAT THIS MECHANISM MAY SUGGEST

IGF-1 LR3 biology is relevant to research involving:

- IGF1R signaling
- muscle-cell proliferation
- tissue growth
- cell culture
- organ growth
- cancer cachexia
- glucose metabolism
- IGFBP biology
- myogenesis
- anabolic signaling
- protein-production systems
- intestinal trophic biology
- receptor pharmacology

ligand bioavailability.

Its strongest experimentally established identity is:

**AN IGF1R-ACTIVE IGF-1 ANALOG WITH MARKEDLY REDUCED IGF-BINDING-PROTEIN AFFINITY.**

# WHAT THIS MECHANISM DOES NOT PROVE

IGF-1 LR3 biology does not prove that:

- LR3 is simply “stronger IGF-1”
- “Long” proves a 20-72-hour human plasma half-life
- reduced IGFBP binding is automatically beneficial
- increased cell proliferation predicts safe human muscle growth
- injecting near a muscle creates localized growth
- increased lean mass equals skeletal-muscle hypertrophy
- LR3 safely improves athletic performance
- LR3 is just long-acting native IGF-1
- LR3 has better intrinsic IGF1R potency than native IGF-1
- IGFBPs are merely unwanted inhibitors
- LR3 selectively targets skeletal muscle
- increased organ growth is beneficial
- increased muscle mass equals improved strength
- LR3 repairs tendons

- LR3 regenerates cartilage
- LR3 is equivalent to mecasermin
- animal nitrogen-retention evidence proves human performance benefit
- serum IGF-1 assays necessarily measure LR3 accurately
- bypassing IGFBPs makes LR3 physiologically superior
- LR3 reverses aging
- mecasermin clinical evidence applies to LR3
- low endogenous IGF-1 during LR3 exposure means total IGF signaling is low
- tumor biology is irrelevant because the target is muscle

every product labeled IGF-1 LR3 contains the correct analog.

**Again:**

**IGF1R SIGNALING + IGFBP ESCAPE + SYSTEMIC DISTRIBUTION + FEEDBACK + GLUCOSE + TISSUE CONTEXT MATTER.**

# THE EVIDENCE, POTENTIAL APPLICATIONS, AND LIMITATIONS

## MOLECULAR IDENTITY

### STRONG

Long R3 IGF-I contains:

• a 13-amino-acid N-terminal extension

• Arg substitution at position 3 of the IGF-I domain

for a total:

**83-AMINO-ACID ANALOG.**

## REDUCED IGFBP AFFINITY

### VERY STRONG

This is the defining biochemical property.

Studies describe dramatically reduced IGFBP binding while retaining activity at the IGF-I receptor.

## IGF1R ACTIVATION

### STRONG

LR3 remains an active IGF1R ligand.

However:

its greater biological effect in many systems appears to depend heavily on:

**REDUCED IGFBP SEQUESTRATION**

rather than simply superior intrinsic receptor agonism.

**CELL-CULTURE GROWTH FACTOR**

**VERY STRONG PRACTICAL / RESEARCH USE**

Long R3 IGF-I is widely used in serum-free and low-serum mammalian cell culture because reduced IGFBP interaction improves growth-factor availability.

## MUSCLE-CELL BIOLOGY

**MEANINGFUL PRECLINICAL / CELLULAR EVIDENCE**

LR3 can stimulate:

• myoblast proliferation

• differentiation-related signaling

in experimental systems.

## ANIMAL ORGAN GROWTH

**DIRECT PRECLINICAL EVIDENCE**

Guinea-pig infusion increased relative weights of several organs without producing overall growth improvement.

## ENDOCRINE FEEDBACK

**DIRECT PRECLINICAL EVIDENCE**

Pig studies demonstrated reductions in:

**GH**

• endogenous IGF-I

### IGFBP-3

• insulin

during LR3 exposure.

**INTESTINAL TROPHIC EFFECTS**

### PRECLINICAL

Neonatal-rat studies demonstrated increased villus growth and intestinal-cell number following Long R3 IGF-I exposure.

**MUSCLE PRESERVATION IN CACHEXIA MODELS**

**PRECLINICAL, WITH IMPORTANT TRADEOFF**

LR3 limited muscle loss in a cancer-cachexia model but accelerated tumor growth.

**HUMAN THERAPEUTIC OUTCOME EVIDENCE**

### VERY LIMITED

There is not a mecasermin-like human therapeutic evidence base establishing LR3 for:

- severe IGF deficiency
- muscle wasting
- sarcopenia
- injury repair

body recomposition.

**HUMAN PHARMACOKINETICS**

### POORLY CHARACTERIZED

Precise commonly quoted LR3 half-life values are not supported by the same level of direct human PK evidence as:

• mecasermin

### CJC-1295

Ipamorelin.

**Again:**

**DO NOT TURN INTERNET HALF-LIFE NUMBERS INTO ESTABLISHED HUMAN PHARMACOLOGY.**

### PERFORMANCE

**NOT ESTABLISHED**

Strong anabolic signaling does not establish:

**ATHLETIC BENEFIT.**

## LONGEVITY

**NOT ESTABLISHED**

The pathway has fundamental growth-longevity tradeoffs.

• Research

## IGFBP BIOLOGY

This is perhaps LR3's greatest research value.

Because it largely escapes:

**IGFBP CONTROL,**

researchers can ask:

**WHAT DOES IGF1R SIGNALING LOOK LIKE WHEN THE NORMAL BINDING-PROTEIN BRAKE IS GREATLY REDUCED?**

That makes LR3 a powerful:

**MECHANISTIC PROBE.**

## CELL CULTURE

This remains one of its clearest applications.

Biopharmaceutical manufacturing needs:

• cell survival

• predictable growth

reproducibility.

LR3 is well suited to this environment because:

**IGFBP ESCAPE IS AN ADVANTAGE.**

## MUSCLE

Future studies would need to separate:

- myoblast proliferation
- satellite-cell activation
- water
- muscle-fiber hypertrophy
- lean mass

actual strength.

**Again:**

**CELL GROWTH ≠ FUNCTIONAL MUSCLE.**

**LOCAL VS SYSTEMIC DELIVERY**

One of the most important future questions is:

**CAN IGF1R SIGNALING BE TARGETED TO MUSCLE WITHOUT EXPOSING THE ENTIRE BODY?**

That may ultimately matter more than:

creating even more potent IGF analogs.

## CACHEXIA

LR3 demonstrated the potential to preserve muscle in animal cancer cachexia.

But the tumor-growth result highlights the major challenge:

**HOW DO YOU STIMULATE HOST TISSUE WITHOUT STIMULATING THE TUMOR?**

This is a systems problem.

## CANCER

Future work needs:

- tumor-specific IGF1R profiles
- tissue targeting
- ligand delivery control

receptor-selective strategies.

**Again:**

**SYSTEMIC GROWTH-FACTOR THERAPY MAY BE TOO BROAD FOR SOME DISEASE CONTEXTS.**

## GLUCOSE

Human studies would need to characterize:

- fasting glucose
- insulin
- hypoglycemia incidence
- CGM patterns
- C-peptide

under controlled exposure.

## IGF ASSAYS

Future analytical work should clarify:

- which clinical IGF-1 assays cross-react with LR3
- whether LR3 can be measured directly

how endogenous IGF suppression should be interpreted.

This is essential for:

**REAL MONITORING.**

# WHAT WE KNOW

IGF-1 LR3 is an 83-amino-acid analog of human IGF-1.

It differs from native 70-amino-acid IGF-1 through a 13-amino-acid N-terminal extension and replacement of glutamic acid at position 3 of the IGF-I portion with arginine.

Those modifications dramatically reduce the analog's affinity for the normal IGF-binding-protein system.

The molecule nevertheless retains biological activity at IGF1R.

That means LR3 does not introduce an entirely new growth pathway.

It changes:

**HOW AVAILABLE THE IGF SIGNAL IS TO THE EXISTING RECEPTOR.**

This is the defining difference from native IGF-1.

Native IGF-1 is strongly buffered by IGFBPs.

LR3 is much harder for that regulatory system to sequester.

This can increase biological activity in settings where IGFBPs would otherwise limit native IGF-1.

That is why Long R3 IGF-I became particularly useful as a serum-free or low-serum cell-culture supplement.

However, reduced IGFBP binding should not be confused with simply having a stronger IGF1 receptor.

Direct receptor studies suggest that LR3 is not necessarily intrinsically more potent than native recombinant IGF-1 at IGF1R under equimolar conditions.

Its apparent potency can instead arise from greater access to the receptor because the binding proteins are less able to sequester it.

That distinction is fundamental:

**RECEPTOR POTENCY**

is not the same as:

**BIOAVAILABLE POTENCY.**

LR3 also demonstrates why growth-factor biology cannot be reduced to skeletal muscle.

Animal infusion studies have demonstrated increases in relative weight of multiple organs including gut, kidney, spleen, and adrenal tissue.

That confirms the systemic nature of the signal.

Another animal study found that LR3 exposure reduced endogenous GH, endogenous IGF-I, IGFBP-3, insulin, food intake, and growth rate.

This shows that pharmacological IGF signaling can trigger significant feedback throughout the GH-IGF system.

The body does not simply add the exogenous signal on top of normal physiology.

It reorganizes the endogenous axis around that signal.

LR3 can also produce powerful tissue-trophic effects.

Animal intestinal studies demonstrated increased villus growth and cell number.

Muscle-cell experiments demonstrate biologically meaningful myogenic signaling.

But these findings should not automatically be converted into human claims of muscle hypertrophy, gut regeneration, injury healing, or athletic enhancement.

Perhaps the most important cautionary preclinical finding comes from cancer cachexia.

LR3 reduced muscle loss in a mouse cachexia model but also accelerated tumor growth.

This is not proof that:

**LR3 CAUSES HUMAN CANCER.**

It proves something more fundamental:

**A SYSTEMIC GROWTH SIGNAL CAN STIMULATE BOTH THE TISSUE YOU WANT TO GROW AND THE TISSUE YOU DO NOT WANT TO GROW.**

That is the central clinical challenge.

# WHAT WE THINK MAY BE HAPPENING

IGF-1 LR3 may be best understood as:

**AN EXPERIMENT IN REMOVING A PHYSIOLOGICAL BRAKE.**

Native IGF-1 is powerful.

So the body does not simply release it freely.

It creates:

**BINDING PROTEINS.**

**IGFBP-3.**

**ALS.**

Other IGFBPs.

The signal is:

• wrapped,

• transported,

• buffered,

and released under:

**CONTROLLED CONDITIONS.**

Then peptide engineering says:

**WHAT IF WE MAKE IGF-1 HARDER FOR THOSE PROTEINS TO HOLD?**

Change position 3.

Add 13 amino acids.

Now:

the receptor still understands:

**IGF SIGNAL.**

But the binding proteins have much more difficulty controlling:

**WHERE AND WHEN THAT SIGNAL BECOMES AVAILABLE.**

In cell culture:

that is fantastic.

The goal is:

**MORE CELL GROWTH.**

In a human body:

that becomes much more complicated.

Because:

the muscle sees the signal.

But so does:

the gut.

The kidney.

The spleen.

Potential tumor tissue.

Vascular cells.

Bone.

Nervous tissue.

Meanwhile:

the hypothalamus and pituitary detect:

**HIGH IGF SIGNALING.**

So GH falls.

Native IGF-1 falls.

Binding proteins may change.

Insulin changes.

Food intake may change.

The entire axis begins:

**REBALANCING ITSELF.**

So LR3 is not:

**“IGF-1 PLUS.”**

It is:

**A DIFFERENT REGULATORY STATE OF THE IGF SYSTEM.**

That is the deeper biology.

# WHAT REMAINS CONTEXT-DEPENDENT

Important questions include:

What is the true human pharmacokinetic profile of IGF-1 LR3?

What is its true plasma half-life?

How much faster does it leave plasma for tissue because of reduced IGFBP binding?

How much of the commonly quoted long half-life is marketing extrapolation?

How long does receptor signaling actually remain elevated?

Is tissue exposure longer than plasma exposure?

Which tissues accumulate LR3 most strongly?

Does skeletal muscle receive preferential exposure?

Does local injection meaningfully alter tissue concentration?

For how long?

Does local administration ever remain truly local?

Which IGFBP interactions are most reduced?

### IGFBP-1?

### IGFBP-2?

### IGFBP-3?

### IGFBP-4?

### IGFBP-5?

### IGFBP-6?

Does weak binding eliminate all IGFBP regulation or merely reduce it?

Can sufficiently high IGFBP concentrations still inhibit LR3?

How much does IGFBP proteolysis matter for LR3?

Does PAPP-A still influence the analog?

What is the exact affinity of LR3 for IGF1R relative to native IGF-1?

Does receptor signaling differ qualitatively?

Does LR3 produce different IGF1R conformations?

Different receptor internalization?

β-subunit phosphorylation?

Different IRS recruitment?

Different PI3K/MAPK balance?

Does it exhibit signaling bias?

Does LR3 activate insulin-receptor isoforms at high concentrations?

How strongly?

Does it bind hybrid IGF1R/insulin receptors?

Does that change glucose effects?

What is the human hypoglycemia risk?

How rapidly would glucose fall?

Does fasting increase risk?

Does carbohydrate intake modify exposure?

Does insulin change LR3 signaling?

Can endogenous insulin and LR3 create additive AKT signaling?

Does repeated exposure suppress endogenous GH in humans?

By how much?

Does endogenous IGF-1 decline?

Does IGFBP-3 decline?

Does ALS decline?

How quickly does the axis recover after discontinuation?

Does prolonged feedback reduce pituitary GH reserve?

Does native IGF-1 rebound?

What is the effect on GH pulsatility?

Does somatostatin increase?

Does GHRH decrease?

Does repeated exposure alter insulin?

Food intake?

appetite?

Does LR3 increase skeletal-muscle protein synthesis in humans?

Does it increase actual fiber cross-sectional area?

Satellite-cell activity?

Does it increase type-I versus type-II fibers differently?

Does resistance exercise potentiate LR3 effects?

Does protein intake matter?

Does caloric surplus matter?

Does muscle growth exceed organ growth?

Can muscle-specific delivery improve that ratio?

Does systemic LR3 increase heart mass?

renal mass?

gut mass?

spleen mass?

thyroid?

lymphoid tissue?

Are those changes reversible?

Does organ enlargement correspond to improved function?

Or simply hypertrophy?

Does LR3 increase muscle strength?

Tendon strength?

Does muscle growth outpace tendon adaptation?

Could rapid muscle hypertrophy increase injury risk?

Does LR3 increase collagen synthesis?

Does it improve tendon healing?

Does it create disorganized matrix?

Does it improve bone density?

Does it accelerate bone turnover?

Does it affect cartilage?

Does it improve fracture healing?

Does it influence peripheral nerve regeneration?

Does it penetrate the CNS?
Could it improve neuronal survival?
Could systemic exposure produce unwanted brain effects?
How does LR3 affect cancer cells with high IGF1R?
Which tumor types are most responsive?
How much does insulin-receptor-A signaling matter in tumors?
Can tumors switch receptor pathways?
Does LR3 accelerate occult tumor growth?
Could tissue-targeted LR3 avoid this?
Is there a safe cancer-history phenotype for IGF analog research?
Can muscle-specific delivery eliminate systemic proliferative exposure?
Does LR3 preserve muscle in non-cancer cachexia?
COPD cachexia?
chronic inflammatory disease?
severe burns?
Does muscle benefit outweigh organ-growth risk?
How do inflammatory cytokines alter LR3 signaling?
Does TNF-α create IGF resistance?
Does reduced IGFBP binding overcome inflammation-induced resistance?
What happens to mTOR under chronic exposure?
Does mTOR feedback eventually reduce insulin signaling?
Could chronic LR3 produce insulin resistance despite acute insulin-like effects?
Does repeated exposure cause receptor downregulation?
How rapidly?
Does IGF1R internalize more with LR3 than native IGF-1?
Does receptor desensitization reduce long-term effectiveness?
Could intermittent exposure preserve signaling?
Does that have any clinical benefit?
Can serum IGF-1 assays detect LR3?
Which commercial assays cross-react?
Could measured IGF-1 appear artificially high?
artificially low?
How should IGFBP-3 be interpreted?
Is there a direct LC-MS method for LR3 quantification?
Could analog-specific monitoring be developed?
How can product identity be verified?
Is the 13-aa extension intact?
Is Arg3 correct?
Are disulfide bonds correctly formed?
Does misfolded LR3 retain activity?
Could aggregates become immunogenic?

What is the stability of reconstituted LR3?

How does oxidation alter receptor activity?

Can analog preparations contain native IGF-1 contaminants?

What percentage of commercial products actually contain the correct 83-aa protein?

Can future IGF analogs retain muscle benefits while restoring some IGFBP regulation?

Could reversible IGFBP affinity be tuned rather than eliminated?

Could tissue-specific prodrugs be developed?

Could muscle-targeting antibodies or nanoparticles localize the signal?

Could receptor-biased IGF analogs separate anabolic from mitogenic signaling?

Can PI3K/AKT signaling be favored over MAPK?

Would that improve safety?

Could local gene expression be safer than systemic protein delivery?

Would DES provide better local pharmacology than LR3?

Or merely different unregulated IGF biology?

**Again:**

these are the questions needed to move from:

**BINDING-PROTEIN-RESISTANT IGF ANALOG**

to:

**PRECISION IGF1R PHARMACOLOGY.**

# THE PRAXIS LENS

**DO NOT BEGIN WITH IGF-1 LR3**

Begin with:

WHY IS IGF1R SIGNALING BEING TARGETED, WHY IS NATIVE IGF-BINDING-PROTEIN REGULATION BEING BYPASSED, AND WHAT TISSUES WILL RECEIVE THE SIGNAL BESIDES THE ONE WE INTEND TO TARGET?

**Then:**

**PHYSIOLOGY**

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

## PHYSIOLOGY

Normal IGF physiology includes:

**GH**

• liver IGF-1 production

• local IGF-1

## IGFBP-1-6

## IGFBP-3

## ALS

• IGFBP proteases

## IGF1R

• insulin receptor

• nutrient availability

tissue-specific receptor expression.

LR3 deliberately changes:

**THE BINDING-PROTEIN COMPONENT.**

**Again:**

**THAT IS NOT A MINOR MODIFICATION.**

## PATTERN

What is actually present?

documented IGF deficiency?

sarcopenia?

cachexia?

muscle injury?

poor training response?

severe malnutrition?

active malignancy?

glucose instability?

normal physiology with performance goals?

**Again:**

**“I WANT MORE ANABOLISM” IS NOT A DIAGNOSIS.**

### MECHANISM

Ask:

Why is the system not growing appropriately?

Could be:

- inadequate mechanical load
- low energy
- GH resistance
- impaired IGF1R
- denervation
- insufficient protein
- low GH
- low native IGF-1
- inflammation

malignancy-driven cachexia.

If the problem is:

**NO TRAINING STIMULUS,**

LR3 does not replace one.

If the problem is:

**MALNUTRITION,**

LR3 does not provide substrate.

If the problem is:

**ACTIVE CANCER,**

broad IGF1R activation may become particularly problematic.

**Again:**

**TARGET THE LIMITING NODE.**

## EVIDENCE

Ask:

**WHAT CLAIM ARE WE MAKING?**

LR3 is an 83-aa IGF-1 analog?

### STRONG.

It has an Arg3 substitution and 13-aa N-terminal extension?

**YES.**

Its IGFBP affinity is dramatically reduced?

**VERY STRONG.**

It retains IGF1R activity?

**YES.**

It is intrinsically a dramatically stronger IGF1R agonist than native IGF-1?

**NOT NECESSARILY.**

Its apparent potency is heavily influenced by:

**REDUCED BINDING-PROTEIN SEQUESTRATION.**

It stimulates myogenic cells?

**YES - PRECLINICAL / CELLULAR.**

It causes tissue growth in animals?

**YES.**

Does it reliably build selective skeletal muscle in humans?

**NOT ESTABLISHED.**

Does it safely improve athletic performance?

**NOT ESTABLISHED.**

Does it improve human recovery?

**NOT ESTABLISHED.**

Does it have a validated human 20-72-hour half-life?

**NOT ADEQUATELY ESTABLISHED.**

**Again:**

**KEEP THE CLAIM WHERE THE DATA ARE.**

# RISK

The central concern is:

**SYSTEMIC GROWTH-FACTOR SIGNALING WITH REDUCED PHYSIOLOGICAL BUFFERING.**

Potential mechanism-based concerns include:

- hypoglycemia
- edema / tissue growth
- feedback suppression of endogenous GH / IGF-1
- growth of tissue outside the intended target
- unwanted organ growth
- IGF1R-driven proliferative signaling
- altered insulin physiology
- tumor-growth concerns in susceptible contexts

product identity / folding / purity.

**Again:**

**THE CENTRAL QUESTION IS NOT WHETHER IGF1R CAN BUILD TISSUE.**

It can.

The question is:

**WHICH TISSUE?**

# MONITORING

Monitoring is particularly difficult because LR3 may disrupt the usual relationship between:

**SERUM IGF-1**

and:

**TOTAL IGF1R SIGNALING.**

## GLUCOSE

Potentially important:

• fasting glucose

• CGM where appropriate

• symptoms of hypoglycemia

## IGF SYSTEM

Potentially:

**IGF-1**

## IGFBP-3

## GH

but interpret cautiously because:

**ASSAY CROSS-REACTIVITY + FEEDBACK MATTER.**

## TARGET TISSUE

If muscle is the claim:

| | |
|---|---|
| • circumference is poor evidence | • DEXA is better |
| • imaging is better | • strength testing matters |

## UNWANTED TISSUE

Mechanistically relevant surveillance includes:

• organ / soft-tissue symptoms

• cardiometabolic context

oncologic history where relevant.

### NUTRITION

• protein

• energy

glucose stability.

**Again:**

**MONITORING SHOULD ASK WHETHER GROWTH OCCURRED WHERE YOU WANTED IT - AND WHETHER IT ALSO OCCURRED WHERE YOU DID NOT.**

## THE PRAXIS 5

### MECHANISM

### IGF-1 LR3:

ARG3 + 13-AA EXTENSION → IGFBP BINDING ↓↓↓ → IGF1R ACCESS ↑ → PI3K/AKT/mTOR + MAPK SIGNALING.

Its defining identity is:

**REDUCED-BUFFERING IGF1R AGONISM.**

## EVIDENCE

Molecular design:

**STRONG.**

Reduced IGFBP affinity:

**VERY STRONG.**

IGF1R activity:

**STRONG.**

Cell-culture growth activity:

**VERY STRONG.**

Muscle-cell biology:

**PRECLINICALLY MEANINGFUL.**

Animal tissue growth:

**DIRECT EVIDENCE.**

Human therapeutic efficacy:

**VERY LIMITED.**

Human performance:

**NOT ESTABLISHED.**

Human long-term safety:

**NOT WELL CHARACTERIZED.**

# RISK

The biggest conceptual errors are:

### 1. ASSUMING ESCAPING IGFBPs MAKES LR3 PHYSIOLOGICALLY SUPERIOR.

**2. ASSUMING GROWTH-FACTOR SIGNALING IS MUSCLE SPECIFIC.**

**3. ASSUMING "LONG" MEANS A PROVEN MULTI-DAY HUMAN HALF-LIFE.**

**4. BORROWING NATIVE IGF-1 OR MECASERMIN CLINICAL EVIDENCE FOR A DIFFERENT ANALOG.**

**Again:**

**MOLECULAR ENGINEERING CHANGES THE EVIDENCE REQUIREMENT - IT DOES NOT LOWER IT.**

# MONITORING

Do not rely only on:

**TOTAL SERUM IGF-1.**

The analog may:

• suppress endogenous IGF

• alter IGFBPs

be variably detected by assays.

Instead monitor:

**THE TARGET FUNCTION + GLUCOSE + WHOLE-BODY TISSUE EFFECTS + AXIS FEEDBACK.**

**Again:**

**THE MORE THE ANALOG DEPARTS FROM NORMAL PHYSIOLOGY, THE MORE IMPORTANT DIRECT OUTCOME MONITORING BECOMES.**

# PATIENT CONTEXT

A patient with:

**SEVERE PRIMARY IGF-1 DEFICIENCY**

is not automatically an LR3 patient.

That condition has:

**NATIVE RECOMBINANT IGF-1 - MECASERMIN - CLINICAL EVIDENCE.**

A healthy athlete is a completely different:

**EVIDENCE + RISK CONTEXT.**

A patient with:

**ACTIVE MALIGNANCY**

is different again.

A patient with:

**CACHEXIA**

• may appear mechanistically attractive for anabolic signaling,

but preclinical tumor findings make:

**DISEASE CONTEXT CRITICAL.**

**Again:**

**SAME RECEPTOR. DIFFERENT CONSEQUENCE.**

# SEVEN QUESTIONS TO ASK BEFORE IGF-1 LR3

**1. WHY IS IGF1R BEING TARGETED DIRECTLY?**

Why bypass:

**GHRH**

**GH**

• hepatic IGF production

much of IGFBP regulation?

**2. WHY LR3 RATHER THAN NATIVE IGF-1?**

What benefit is expected from:

**REDUCING IGFBP CONTROL?**

**3. WHICH TISSUE IS THE TARGET?**

muscle?

gut?

bone?

nervous tissue?

And:

**WHAT OTHER TISSUES WILL RECEIVE THE SAME SIGNAL?**

**4. WHAT IS THE MALIGNANCY CONTEXT?**

Because:

IGF1R is:

**A GROWTH + SURVIVAL RECEPTOR.**

**5. WHAT IS THE GLUCOSE CONTEXT?**

Because:

IGF signaling can be:

**INSULIN-LIKE.**

### 6. HOW WILL EXPOSURE BE MONITORED?

If standard IGF-1 assays do not reliably quantify LR3:

what biomarker actually tells us:

### HOW MUCH SIGNAL IS PRESENT?

### 7. WHAT WOULD DEFINE SUCCESS?

Not:

### “IGF SIGNALING IS HIGH.”

Not:

### “LEAN MASS WENT UP.”

**But:**

THE SPECIFIC TARGET TISSUE OR FUNCTION IMPROVED IN A MEASURABLE WAY - FOR EXAMPLE TRUE SKELETAL-MUSCLE MASS AND STRENGTH - WHILE GLUCOSE, ENDOGENOUS GH/IGF FEEDBACK, ORGAN EFFECTS, PROLIFERATIVE RISK, AND WHOLE-PATIENT PHYSIOLOGY REMAINED ACCEPTABLE.

# KEY TAKEAWAYS

IGF-1 LR3 is an 83-amino-acid analog of human IGF-1.

It contains a 13-amino-acid N-terminal extension and substitutes arginine for glutamic acid at position 3 of the IGF-I domain.

Those modifications dramatically reduce interaction with IGF-binding proteins while preserving IGF1R activity.

That is:

**THE DEFINING PHARMACOLOGY.**

• LR3 should not simply be called “stronger IGF-1.”

Its greater biological activity in many systems appears largely because:

**MORE LIGAND REMAINS AVAILABLE TO THE RECEPTOR**

rather than because IGF1R necessarily responds more strongly to each molecule.

This distinction between receptor potency and bioavailability is essential.

LR3 was developed and remains widely useful as a cell-culture growth factor because cells secrete IGFBPs that can neutralize native IGF-1.

By escaping that regulation, LR3 can promote more consistent cell proliferation and viability.

**But:**

**A BIOREACTOR AND A HUMAN BODY HAVE DIFFERENT GOALS.**

A bioreactor wants:

**MORE CELL GROWTH.**

A human wants:

**THE RIGHT TISSUE GROWING AT THE RIGHT TIME.**

That distinction changes everything.

Animal studies make the systemic nature of LR3 clear.

Long R3 IGF-I increased the relative size of several organs in guinea pigs, including the gut, kidneys, spleen, and adrenals, without producing simple overall growth enhancement.

In pigs, LR3 altered the entire endocrine system, lowering endogenous GH, endogenous IGF-I, IGFBP-3, insulin, and food intake.

This demonstrates:

**EXOGENOUS SIGNAL DOES NOT SIMPLY ADD TO ENDOGENOUS SIGNAL.**

## THE SYSTEM FEEDS BACK.

LR3 also produces real anabolic and trophic effects in preclinical muscle and intestinal systems.

**But:**

**CELL GROWTH ≠ HUMAN MUSCLE HYPERTROPHY.**

**TISSUE TROPHISM ≠ SELECTIVE REGENERATION.**

**ANABOLIC SIGNALING ≠ ATHLETIC PERFORMANCE.**

And perhaps most importantly:

**A SYSTEMIC GROWTH FACTOR DOES NOT KNOW WHICH TISSUE YOU INTENDED TO GROW.**

The cancer-cachexia model makes that point unmistakably.

LR3 reduced muscle wasting but was accompanied by accelerated tumor growth.

That does not mean:

LR3 automatically causes cancer.

It means:

**THE SAME GROWTH SIGNAL CAN BENEFIT ONE TISSUE AND SUPPORT AN UNWANTED TISSUE AT THE SAME TIME.**

That is the central risk of systemic growth-factor pharmacology.

• Another common misunderstanding involves the word “Long.”

It refers to:

**THE N-TERMINAL EXTENSION.**

It should not be treated as proof of a specific:

**20-, 30-, 56-, OR 72-HOUR HUMAN HALF-LIFE.**

Direct human LR3 pharmacokinetic evidence is not robust enough to support the certainty with which those numbers are commonly repeated online.

Moreover:

**IGFBP BINDING ITSELF PROLONGS NATIVE IGF CIRCULATION.**

**So:**

reduced binding can increase:

**TISSUE BIOAVAILABILITY**

without automatically increasing:

**PLASMA HALF-LIFE.**

**Again:**

**BIOLOGICAL PERSISTENCE ≠ BLOOD HALF-LIFE.**

That is one of the most important corrections in this entire guide.

# THE BOTTOM LINE

IGF-1 LR3 is often introduced as:

**“A LONGER-ACTING, MORE POWERFUL IGF-1 FOR MUSCLE GROWTH.”**

That description is too shallow.

The real story is much more interesting.

Native IGF-1 is powerful.

So the body builds:

**A CONTROL SYSTEM AROUND IT.**

IGFBPs.

**ALS.**

Local proteases.

Transport.

Reservoirs.

Release.

The body does not want:

**FREE, UNCONTROLLED GROWTH SIGNAL EVERYWHERE.**

Then researchers create:

**LONG R3 IGF-1.**

Change position 3.

Add 13 amino acids.

Now:

the IGF receptor still recognizes the molecule.

**But:**

the binding proteins do not control it nearly as effectively.

That makes the signal:

**MORE AVAILABLE.**

And in a cell-culture flask:

that is tremendously useful.

Cells grow.

They survive.

They produce more recombinant protein.

Excellent.

But now place the same idea into:

**A HUMAN BODY.**

Muscle sees the signal.

But so do:

kidneys.

gut.

spleen.

heart.

bone.

vascular cells.

potential tumor tissue.

And the endocrine system notices:

**IGF SIGNAL IS HIGH.**

**So:**

GH can fall.

Native IGF-1 can fall.

IGFBP-3 can change.

Insulin can change.

The system reorganizes.

That means LR3 is not simply:

**MORE IGF-1.**

It is:

**A DIFFERENT VERSION OF THE IGF SYSTEM.**

One in which:

**THE BINDING-PROTEIN BRAKE HAS BEEN GREATLY WEAKENED.**

And that is why the most important question is not:

**“HOW ANABOLIC IS LR3?”**

We already know IGF1R is anabolic.

The more important questions are:

**WHERE DOES THE SIGNAL GO?**

**HOW LONG DOES THE TISSUE SEE IT?**

**WHAT HAPPENS TO GLUCOSE?**

**WHAT HAPPENS TO ENDOGENOUS GH AND IGF-1?**

## WHAT HAPPENS TO ORGANS?

**WHAT HAPPENS TO UNWANTED CELLS?**

**DOES MUSCLE FUNCTION ACTUALLY IMPROVE?**

And:

**CAN WE MEASURE THE ANALOG ACCURATELY ENOUGH TO KNOW WHAT EXPOSURE WE CREATED?**

That is where peptide medicine becomes:

**SYSTEMS MEDICINE.**

So the Praxis question becomes:

“WHY is IGF1R signaling being increased directly, why is normal IGF-binding-protein regulation being bypassed, which tissue is actually the intended target, which other tissues will inevitably receive the same growth signal, how will glucose and endogenous GH-IGF feedback respond, and does the measurable functional benefit justify creating a systemic IGF environment that is deliberately less constrained than native human physiology?”

That is the difference between:

**CALLING IGF-1 LR3 A STRONGER MUSCLE-BUILDING IGF**

and:

**UNDERSTANDING BINDING-PROTEIN-RESISTANT IGF1R PHARMACOLOGY.**

# FINAL RECALL

| DECODE | CONTROL | VERIFY |
|---|---|---|
| **Long = extension; R3 = Arg at position 3** | **IGFBP escape changes the whole regulatory state** | **Measure function, glucose, feedback, and unintended 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 LR3 is an engineered 83-amino-acid IGF-1 analog designed to retain IGF1R activity while markedly reducing interaction with normal IGF-binding proteins. Its strongest evidence concerns molecular pharmacology, cell-culture biology, receptor signaling, and preclinical tissue effects. Human therapeutic, performance, body-composition, and long-term safety data are much less developed than the evidence for native IGF-1 or mecasermin, and commonly repeated claims about prolonged human half-life should not be treated as established without direct pharmacokinetic evidence.