



PRAXIS
PEPTIDE INSTITUTE

IGF-1 DES

ADVANCED MECHANISM AND EVIDENCE GUIDE

TRUNCATED IGF-1 SIGNAL WITH REDUCED BINDING-PROTEIN RESTRAINT
67 amino acids • des(1-3) • IGFBP escape • IGF1R • PI3K-AKT-mTOR • MAPK • growth • metabolism

MEMORY KEY: IGF-1 DES DOES NOT CREATE A NEW RECEPTOR - IT REMOVES THREE RESIDUES THAT NORMALLY HELP CONTROL ACCESS.

Educational monograph • Strong molecular and cellular 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 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 Des; the remaining pages add mechanism, evidence, context, and nuance.

01	IDENTITY A naturally occurring 67-amino-acid IGF-1 form created by removing the N-terminal Gly-Pro-Glu tripeptide.
02	ACCESS Retains IGF1R affinity while binding IGFBPs far less strongly, increasing receptor-accessible ligand.
03	SIGNAL Activates IGF1R tyrosine-kinase pathways including IRS-PI3K-AKT-mTOR and SHC-RAS-MAPK.
04	POTENCY Greater cellular effect often reflects escape from sequestration, not a fundamentally better receptor interaction.
05	LOCALITY Local tissue biology is plausible, but injection location does not guarantee tissue confinement.
06	SYSTEM Muscle, gut, brain, glucose, organs, feedback loops, and proliferative tissues can all encounter IGF signaling.
07	EVIDENCE Molecular and preclinical support is much stronger than validated human hypertrophy, recovery, or longevity outcomes.
08	PRAXIS QUESTION Why bypass IGFBP control, what tissue is targeted, what else sees the signal, and did function improve safely?

ONE-SENTENCE MEMORY

IGF-1 DES DOES NOT CREATE A NEW RECEPTOR - IT REMOVES THREE RESIDUES THAT NORMALLY HELP CONTROL ACCESS.

UNDERSTAND THE PEPTIDE

IGF-1 DES - more precisely Des(1-3) IGF-1 - is a naturally occurring truncated form of insulin-like growth factor-1 in which the first three amino acids of native IGF-1 have been removed.

Native human IGF-1 contains:

70 AMINO ACIDS.

The N-terminal sequence begins:

GLY-PRO-GLU

or:

GPE.

IGF-1 DES removes those first:

THREE RESIDUES.

So:

- 70-aa IGF-1

minus:

Gly¹-Pro²-Glu³



67-AMINO-ACID DES(1-3) IGF-1.

That sounds like a very small structural change.

Only:

THREE AMINO ACIDS.

But those three residues play a disproportionately important role in:

IGF-BINDING-PROTEIN INTERACTION.

The result is a molecule that still binds:

IGF1R

but interacts much less strongly with:

IGF-BINDING PROTEINS - IGFBPs.

Classic biochemical studies found that the N-terminal region of IGF-1 is critical for IGFBP binding while receptor affinity can be largely retained after the first three amino acids are removed.

That is the defining pharmacology.

The best conceptual description is:

IGF-1 DES IS A TRUNCATED IGF-1 SIGNAL THAT RETAINS RECEPTOR ACTIVITY WHILE ESCAPING MUCH OF THE NORMAL BINDING-PROTEIN RESTRAINT THAT REGULATES NATIVE IGF-1.

That should immediately sound familiar.

Because:

IGF-1 LR3

and:

IGF-1 DES

were both discussed as ways of altering:

IGFBP CONTROL.

But they do it differently.

LR3:

ADDS + SUBSTITUTES.

DES:

REMOVES.

THE CENTRAL STRUCTURAL CHANGE

Native IGF-1:

70 aa



N-terminus begins:

GLY-PRO-GLU



strong IGFBP interaction.

DES(1-3) IGF-1:

remove:

GLY¹

PRO²

GLU³



67 aa



IGFBP affinity drops dramatically

while:

IGF1R affinity remains broadly comparable to native IGF-1.

Again:

THREE AMINO ACIDS CHANGE THE REGULATORY ENVIRONMENT WITHOUT DESTROYING THE CORE RECEPTOR MESSAGE.

WHAT DOES “DES” MEAN?

In peptide nomenclature:

DES

means:

DELETED FROM THE N-TERMINUS.

So:

- Des(1-3) IGF-1

means:

amino acids:

- 1 through 3

have been removed.

It does not mean:

- deactivated
- desiccated
- designer

synthetic-only.

It means:

THE FIRST THREE AMINO ACIDS ARE ABSENT.

IGF-1 DES CAN OCCUR NATURALLY

This is an especially interesting part of the molecule.

Des(1-3) IGF-1 is not solely an invented synthetic analog.

It has been isolated from biological tissues and fluids, including:

- bovine colostrum
- human brain

porcine uterus.

A major review described it as a naturally occurring truncated IGF-1 variant likely generated through:

POST-TRANSLATIONAL CLEAVAGE OF IGF-1.

That matters.

Because it means the body itself may sometimes use:

PROTEOLYTIC PROCESSING

to change:

IGF-1 BIOAVAILABILITY.

Again:

THE BODY CAN MODIFY A PEPTIDE AFTER IT IS MADE TO CREATE A DIFFERENT SIGNALING FORM.

THIS IS PEPTIDE PROCESSING AS REGULATION

Start with:

native IGF-1.

Then:

protease removes:

Gly-Pro-Glu.

Now:

- the same basic growth factor

becomes:

MUCH LESS CONTROLLED BY IGFBPs.

That means the body may regulate not only:

HOW MUCH IGF-1 IS PRODUCED

but also:

WHICH FORM OF IGF-1 EXISTS LOCALLY.

This is a profound systems concept.

PEPTIDE IDENTITY CAN CHANGE AFTER SECRETION

The usual simplistic model:



But real biology often looks like:



Again:

THE MOLECULE YOU START WITH MAY NOT BE THE MOLECULE THAT ACTUALLY SIGNALS IN THE TISSUE.

THE CORE IDENTITY



RAS-MAPK



growth

- survival
 - differentiation
- metabolic signaling.

Again:**DES DOES NOT CREATE A NEW RECEPTOR.**

It changes:

HOW DIFFICULT IT IS FOR BINDING PROTEINS TO KEEP THE LIGAND AWAY FROM THE RECEPTOR.

IGF-1 DES AND IGF1R

Its principal signaling receptor remains:

IGF1R.

IGF1R is a:

RECEPTOR TYROSINE KINASE.

Ligand binding promotes receptor activation and autophosphorylation.

Then:**IGF1R**

IRS proteins



PI3K



AKT

mTOR-related
signaling

protein synthesis

- cell survival
- metabolism.

And:

IGF1R

SHC



RAS



RAF



MEK



ERK



proliferation

- differentiation
- growth.

Again:**IGF-1 DES USES THE SAME CENTRAL GROWTH-FACTOR NETWORK AS NATIVE IGF-1.**

THE DIFFERENCE IS ACCESS

Native IGF-1:

- receptor affinity
- strong IGFBP binding.

DES:

- similar receptor affinity
- weak IGFBP binding.

So the key pharmacological difference is not:

“DOES THE RECEPTOR RECOGNIZE IT?”

Yes.

The important question is:

“HOW MUCH OF THE LIGAND REMAINS AVAILABLE TO REACH THE RECEPTOR?”

IGFBPS ARE THE GATE

Native IGF-1



IGFBPs



sequestration

- transport
 - buffering
- controlled tissue exposure.

DES



weak IGFBP affinity



less sequestration



greater availability.

Again:

THE BIOLOGICAL POTENCY COMES LARGELY FROM ESCAPING THE GATEKEEPER.

HOW MUCH MORE POTENT IS DES?

Classic review literature commonly described Des(1-3) IGF-I as roughly:

10-FOLD MORE POTENT

than native IGF-1 in many cultured-cell hypertrophy and proliferation assays.

Importantly:

that increased apparent potency was attributed largely to:

REDUCED IGFBP BINDING

rather than a dramatically stronger intrinsic interaction with IGF1R.

Again:

APPARENT POTENCY $\neq$ INTRINSIC RECEPTOR POTENCY.

That is the same lesson we saw with:

IGF-1 LR3.

THE RECEPTOR-POTENCY VS BIOAVAILABILITY DISTINCTION

Suppose:

- native IGF-1

and:

DES

bind IGF1R similarly.

But:

native IGF-1 is trapped by IGFBPs.

DES is not.

Then:

DES produces a larger biological effect.

The receptor did not necessarily become:

MORE SENSITIVE.

The ligand became:

MORE AVAILABLE.

Again:

BIOAVAILABILITY CAN MASQUERADE AS RECEPTOR POTENCY.

THE N-TERMINUS IS AN IGFBP INTERFACE

Binding studies demonstrated that residues in the N-terminal B-domain of IGF-1 are critical for binding multiple IGFBPs, while modification in that region can spare IGF-receptor interaction.

This explains why removing:

GPE

has such a dramatic effect.

Again:

THE SAME PEPTIDE SURFACE CAN BE CRITICAL FOR ONE PROTEIN INTERACTION AND DISPENSABLE FOR ANOTHER.

THIS IS MOLECULAR SELECTIVITY BY DELETION

Usually peptide engineering sounds like:

add something.

Modify something.

Attach something.

DES demonstrates another strategy:

REMOVE SOMETHING.

Native peptide → delete regulatory interaction site → receptor still functions → binding-protein interaction collapses.

Again:

LESS MOLECULE CAN PRODUCE MORE BIOLOGICAL SIGNAL.

That is counterintuitive.

And very important.

IGF-1 DES VS NATIVE IGF-1

NATIVE IGF-1

70 amino acids.

Strong IGFBP interaction.

IGF1R agonist.

Highly buffered systemic biology.

IGF-1 DES

67 amino acids.

Gly-Pro-Glu removed.

Weak IGFBP interaction.

IGF1R affinity retained.

Greater activity in many IGFBP-rich experimental systems.

Again:

NATIVE IGF-1 = GROWTH FACTOR WITH STRONG BINDING-PROTEIN CONTROL.

DES = GROWTH FACTOR WITH MUCH LESS BINDING-PROTEIN CONTROL.

IGF-1 DES VS IGF-1 LR3

This is the most important comparison in the guide.

DES(1-3) IGF-1

• 70 aa

minus:

first 3 residues



67 aa.

Naturally occurring truncated form has been identified in biological tissues.

Weak IGFBP binding.

LONG R3 IGF-1

• native IGF-1 domain

• Arg3 substitution

13-aa N-terminal extension



83 aa.

Engineered analog.

Also weak IGFBP interaction.

Again:

both create:

IGFBP-RESISTANT IGF PHARMACOLOGY.

But:

their structures are completely different.

DES REMOVES THE REGULATORY REGION

LR3:

DISTORTS / EXTENDS IT.

DES:

CUTS IT OFF.

That difference could affect:

- | | |
|-----------------------|-------------------|
| • tissue distribution | • clearance |
| • receptor kinetics | • local retention |
| • proteolysis | |

immunogenicity.

Again:

SAME GENERAL DESIGN GOAL $\neq$ SAME MOLECULE.**THE “LOCAL DES” CLAIM**

IGF-1 DES is often marketed as:

“THE LOCAL IGF.”

The idea is that:

DES has:

- very high local activity
- reduced IGFBP binding
- relatively short persistence

and therefore may act more locally than LR3.

There is a reasonable mechanistic basis for thinking about:

LOCAL BIOAVAILABILITY.

But:

the strong internet claim:

“INJECT IT INTO A MUSCLE AND IT ONLY GROWS THAT MUSCLE”

is not established by robust human evidence.

Again:

LOCAL ACTION $\neq$ INJECTION-SITE EXCLUSIVITY.

THE LOCALITY PROBLEM

Local injection → interstitial tissue → capillaries → circulation.

Unless the molecule is specifically:

- tethered
- depot-bound
- receptor-targeted
- rapidly degraded before systemic distribution

some portion can become:

SYSTEMIC.

Again:

NEARBY DOES NOT MEAN CONFINED.

LOCAL BIOLOGY IS STILL IMPORTANT

The more scientifically defensible concept is:

Des(1-3) IGF-I may be particularly active in:

LOCAL IGFBP-RICH TISSUE MICROENVIRONMENTS.

Why?

Because:

native IGF-1 gets restrained locally by:

IGFBP-4

IGFBP-5

IGFBP-6

and others.

DES: → **escapes much of that restraint.**

This has been demonstrated clearly in:

SKELETAL-MUSCLE CELL SYSTEMS.

Again:

MICROENVIRONMENTAL ADVANTAGE $\neq$ INJECTION-SITE EXCLUSIVITY.

IGF-1 DES AND MUSCLE

This is one of the strongest preclinical domains.

Skeletal-muscle cells produce:

IGFBPs.

Those proteins can inhibit:

IGF-1-INDUCED MYOGENESIS.

In rat L6E9 muscle cells:

Des(1-3) IGF-I was substantially more potent than native IGF-I at stimulating differentiation markers.

The investigators concluded that skeletal-muscle-derived IGFBPs restrain native IGF action, whereas DES partially escapes that inhibition.

This is real mechanistic muscle biology.

THE MUSCLE MODEL

Exercise / loading



local IGF system



IGF1R



myogenic signaling.

But:

muscle cells also produce:

IGFBPs



native IGF availability restrained.

DES



weak IGFBP binding



greater IGF1R access



myogenesis signal ↑.

Again:

THE ANALOG DOES NOT CREATE MUSCLE PHYSIOLOGY.

It changes:

THE DEGREE OF REGULATION OF AN EXISTING MUSCLE-GROWTH SIGNAL.

MYOGENESIS

Myogenesis involves:

- satellite-cell activation
- differentiation
- protein synthesis
- myoblast proliferation
- fusion
- mechanical loading

innervation.

IGF1R participates strongly.

DES can increase:

IGF1R-DEPENDENT MYOGENIC SIGNALING

in experimental systems.

But:

CELL DIFFERENTIATION $\neq$ HUMAN MUSCLE HYPERTROPHY PROVEN.

DES MAY BE MORE POTENT THAN NATIVE IGF-1 IN MUSCLE CELLS

This makes sense mechanistically.

Native IGF-I



binds IGFBP-4 and other proteins



receptor access limited.

DES



escapes those proteins



receptor access ↑.

Again:

the improved effect is not necessarily:

A BETTER IGF1R SIGNAL.

It is:

LESS SIGNAL SEQUESTRATION.

IGF-1 DES AND NITROGEN RETENTION

In nitrogen-restricted rats, researchers compared:

- recombinant human IGF-I

Des(1-3) IGF-I.

Both influenced nitrogen balance and protein metabolism, with DES demonstrating potent anabolic activity despite not measurably restoring circulating IGF-I levels in the same way as native IGF-I.

This again illustrates:

SERUM IGF-1 CONCENTRATION $\neq$ TOTAL IGF SIGNALING.

THE SERUM-LAB PARADOX

Give DES.



tissue IGF1R signaling ↑

but:

standard assay may primarily measure:

native IGF-I.

So:

serum IGF-1 might not rise much.

Yet:

biological effect can still occur.

Again:

BIOMARKER CONCENTRATION $\neq$ ANALOG RECEPTOR EXPOSURE.

This makes monitoring especially difficult.

DES AND GUT TISSUE

One of the recurring preclinical observations with Des(1-3) IGF-I is:

STRONG GUT-TROPHIC ACTIVITY.

The major 1996 review noted that DES retained enhanced in-vivo potency and showed particularly evident:

SELECTIVE ANABOLIC EFFECTS IN GUT TISSUES.

This is fascinating.

Because it suggests:

tissues with high local IGFBP activity may respond especially strongly to:

BINDING-PROTEIN-RESISTANT IGF.

THE GUT MAY BE AN IGFBP-RICH TARGET ENVIRONMENT

Intestinal tissue has:

- rapid turnover
- strong growth-factor signaling

abundant local IGF regulation.

So:

DES

reduced IGFBP restraint



potentially strong epithelial / trophic signaling.

Again:

TISSUE RESPONSE DEPENDS ON THE LOCAL REGULATORY ENVIRONMENT.

IGF-1 DES AND INFLAMMATORY BOWEL-DISEASE RESEARCH

Because of:

- trophic gut effects
- anabolic effects
- IGF-system involvement in mucosal repair

Des(1-3) IGF-I was historically proposed as potentially relevant to:

CATABOLIC STATES

and:

INFLAMMATORY BOWEL DISEASE.

However, the major review explicitly noted that clinical opportunities had:

NOT YET BEEN EVALUATED.

That distinction remains important.

Again:

POTENTIAL CLINICAL APPLICATION ≠ COMPLETED CLINICAL EVIDENCE.

GUT GROWTH ≠ BARRIER HEALING PROVEN

- Stronger epithelial growth

may support:

- crypt proliferation
- villus maintenance

mucosal recovery.

But IBD involves:

- | | |
|---------------------|----------------------|
| • immune activation | • cytokines |
| • microbiome | • barrier disruption |
| • fibrosis | |

genetic susceptibility.

Again:

TROPHIC SIGNAL ≠ COMPLETE IBD THERAPY.

IGF-1 DES AND COLON-CANCER CELLS

Here the systems problem becomes obvious.

A human colon-carcinoma cell study used Des(1-3) IGF-I specifically because it:

ESCAPES IGFBP SEQUESTRATION

and can therefore reveal IGF-receptor biology more clearly.

DES promoted differentiation-related changes in the studied colon-carcinoma cell system.

This does not establish:

THERAPEUTIC ANTI-CANCER ACTIVITY.

It demonstrates:

CANCER CELLS CAN RESPOND TO IGF SIGNALING.

Again:

THE SAME RECEPTOR EXISTS IN DISEASED CELLS.

IGF-1 DES AND NEUROBLASTOMA

Human neuroblastoma cell studies also found:

- Des(1-3) IGF-I

to be more potent than native IGF-I in stimulating:

CELL PROLIFERATION

and differentiation-related responses.

Again:

this is biologically informative.

But it reinforces:

SYSTEMIC GROWTH-FACTOR SIGNALING IS NOT MUSCLE SELECTIVE.

THE PROLIFERATIVE-SELECTIVITY PROBLEM

Desired target:

muscle.

But:

IGF1R exists on:

- | | |
|---------------------|--------------------|
| • neural cells | • epithelial cells |
| • tumor cells | • bone |
| • connective tissue | • smooth muscle |

many organs.

DES does not know:

WHICH CELL YOU WANTED TO STIMULATE.

Again:

IGF1R IS A GROWTH RECEPTOR, NOT A MUSCLE RECEPTOR.

IGF-1 DES AND CANCER CONTEXT

The correct statement is not:

“DES CAUSES CANCER.”

That would go beyond the evidence.

The correct statement is:

IGF1R signaling participates in:

- proliferation
- survival
- differentiation

anti-apoptotic signaling.

And:

DES has been shown experimentally to alter growth and differentiation in:

human tumor-cell systems.

Therefore:

MALIGNANCY CONTEXT MATTERS.

Again:

NORMAL GROWTH SIGNALING CAN BE USED BY ABNORMAL CELLS.

IGFBP-3 CAN STILL MATTER EVEN WHEN DES DOES NOT BIND IT WELL

This is one of the most interesting nuances in the entire IGF section.

At first:

DES appears to bypass IGFBP-3 because:

it binds the protein poorly.

But research showed that IGFBP-3 can inhibit:

IGF1R SIGNALING

through mechanisms that are at least partly independent of simply binding the ligand.

IGFBP-3 reduced IGF1R activation even when Des(1-3) IGF-I was used as the ligand.

That is incredibly important.

THE BINDING-PROTEIN STORY IS MORE COMPLEX THAN SEQUESTRATION

The simplistic model:

IGFBP binds IGF



blocks receptor.

But:

IGFBP-3 can also influence:

THE CELL / RECEPTOR ENVIRONMENT ITSELF.

So even an IGF analog that:

DOES NOT BIND IGFBP-3 WELL

may still encounter:

IGFBP-3-MEDIATED REGULATION.

Again:

ESCAPING LIGAND BINDING DOES NOT ESCAPE EVERY FUNCTION OF THE BINDING PROTEIN.

THIS IS A MAJOR PPI LESSON

A regulator can operate:

- directly

bind ligand.

and:

- indirectly

alter receptor environment.

Therefore:

remove one interaction



you may not remove:

THE WHOLE REGULATORY SYSTEM.

Again:

MOLECULAR PATHWAYS ARE REDUNDANT AND MULTILAYERED.

IGF-1 DES AND THE BRAIN

Des(1-3) IGF-I has been used experimentally to distinguish:

- IGF1R binding

from:

- IGFBP binding

in human brain and pituitary tissues because DES retains high receptor affinity but low IGFBP affinity.

That makes DES useful as:

A RECEPTOR-DISSECTION TOOL.

Again:

peptide analogs are not only therapeutic candidates.

They can be:

EXPERIMENTAL PROBES.

PEPTIDE → MECHANISTIC PROBE

Native IGF-I binds:

IGF1R

and:

IGFBPs.

Hard to know which binding site you are measuring.

Add:

DES.

If binding remains:

likely receptor.

If binding disappears:

likely IGFBP-related.

Again:

MODIFIED PEPTIDE → BIOLOGICAL QUESTION → INFORMATION.

This is exactly the sort of reasoning PPI should emphasize.

IGF-1 DES AND NEUROBIOLOGY

IGF1R signaling can support:

- neuronal survival
- differentiation

neurite biology.

DES has demonstrated potent effects in:

neuronal-cell models.

But:

this does not establish:

HUMAN NEUROREGENERATION.

Again:

NEURONAL CELL RESPONSE ≠ RESTORATION OF A HUMAN NERVOUS SYSTEM.

IGF-1 DES AND GLUCOSE

Like native IGF-1:

DES activates:

IGF1R.

Therefore insulin-like metabolic actions are relevant.

Potential:

IGF1R

AKT



glucose uptake ↑



blood glucose may decrease.

At sufficiently high exposure:

interaction with:

- insulin receptor
- IGF1R/insulin hybrid receptors

could also become relevant.

Again:

GROWTH FACTOR SIGNALING AND GLUCOSE SIGNALING ARE NOT SEPARATE SYSTEMS.

HYPOGLYCEMIA IS MECHANISTICALLY PLAUSIBLE

This does not mean precise human DES hypoglycemia rates are known.

They are not.

But:

native IGF-1 has known glucose-lowering biology.

DES preserves:

IGF1R activity.

Therefore:

GLUCOSE LOWERING IS A REASONABLE ON-PATHWAY CONCERN.

Again:

MECHANISTIC RISK CAN EXIST BEFORE PRECISE EVENT RATES ARE KNOWN.

IGF-1 DES AND FEEDBACK

Direct IGF1R activation occurs:

DOWNSTREAM OF GH.

So:

DES can theoretically feed back to:

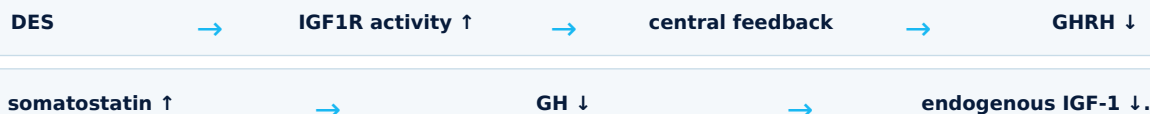
- hypothalamus
 - pituitary
- endogenous GH output.
This is expected from:

THE GH-IGF NEGATIVE-FEEDBACK LOOP.

Again:

ADDING A DOWNSTREAM SIGNAL CAN SUPPRESS UPSTREAM PRODUCTION.

THE FEEDBACK LOOP



Again:

EXOGENOUS IGF SIGNALING CAN REDUCE ENDOGENOUS IGF PRODUCTION INDIRECTLY.

A LOW TOTAL IGF-1 LAB MAY BECOME MISLEADING

- If endogenous IGF-I falls
- while:
- DES is still activating IGF1R,
- serum native IGF-1 could theoretically appear:

LOWER

while:
total pathway signaling remains:

HIGHER.

Again:

ENDOGENOUS CONCENTRATION $\neq$ TOTAL PATHWAY ACTIVITY UNDER ANALOG EXPOSURE.

THE ASSAY PROBLEM

Standard IGF-1 assays may not quantify:

DES

the same way they quantify:
native IGF-1.
Detection depends on:

- antibody epitope
 - extraction method
- analog cross-reactivity.

Therefore:

serum IGF-1 may not reliably tell you:

HOW MUCH DES IS PRESENT.

Again:

MODIFIED MOLECULE CAN BREAK STANDARD MONITORING ASSUMPTIONS.

IGF-1 DES VS MECASERMIN

MECASERMIN

recombinant human IGF-1.

70 aa.

Native sequence.

Established human therapeutic development.

Strong IGFBP interaction.

DES

67 aa.

N-terminal GPE removed.

Reduced IGFBP interaction.

Experimental truncated variant.

Human therapeutic development:

MUCH LESS ESTABLISHED.

Again:

MECASERMIN DATA DO NOT AUTOMATICALLY APPLY TO DES.

DO NOT BORROW PRIMARY IGF-1-DEFICIENCY DATA

Severe primary IGF-1 deficiency



Mecasermin



human therapeutic evidence.

DES



same broad receptor

but:

different:

- sequence
- binding proteins
- tissue availability

pharmacokinetics.

Again:

SAME RECEPTOR $\neq$ SAME THERAPY.

IGF-1 DES VS GH SECRETAGOGUES

This distinction should be extremely clear.

GHRP-6 / GHRP-2 / Ipamorelin → GHSR → pituitary → GH → IGF-1.

Sermorelin / Modified GRF / CJC-1295 / Tesamorelin → GHRHR → pituitary → GH → IGF-1.

DES → DIRECT IGF1R SIGNALING.

Again:

DES BYPASSES TWO UPSTREAM LAYERS.

THE BYPASS COST

Upstream secretagogue:

GHRH/GHSR stimulation → pituitary regulates output → liver regulates IGF → IGFbPs regulate availability.

DES: → direct receptor-active analog

with:

much weaker IGFbP restraint.

Again:

MORE DIRECT SIGNALING = LESS PHYSIOLOGICAL GOVERNANCE.

That is not automatically:

- good

or:

bad.

It simply means:

MORE RESPONSIBILITY SHIFTS TO THE INTERVENTION.

IGF-1 DES AND THE “SHORT HALF-LIFE” CLAIM

You will frequently see extremely precise online statements such as:

20-30 MINUTES

for IGF-1 DES.

But the high-quality direct human pharmacokinetic evidence supporting a single precise DES half-life is:

LIMITED.

The molecule clearly differs pharmacologically from:

- native IGF-1

and:

LR3.

But exact online numbers are often repeated with:

MORE CERTAINTY THAN THE HUMAN DATA SUPPORT.

Again:

DO NOT CONFUSE PEPTIDE-MARKETPLACE CONSENSUS WITH PHARMACOKINETIC EVIDENCE.

IGFBP ESCAPE DOES NOT AUTOMATICALLY PREDICT HALF-LIFE

Remember:

IGFBPs can:

PROLONG IGF CIRCULATION.

So:

- lower binding

can mean:

- greater receptor availability

but potentially:

different / faster tissue distribution and clearance.

Again:

MORE POTENT LOCALLY $\neq$ LONGER-LIVED IN PLASMA.

THE “DES IS LOCAL, LR3 IS SYSTEMIC” CLAIM

There is some mechanistic basis for comparing their:

- binding-protein interaction
- tissue availability

- duration

differently.

But reducing the molecules to:

DES = LOCAL

and:

LR3 = SYSTEMIC

is too simplistic.

Both can potentially reach:

SYSTEMIC CIRCULATION.

The exact spatial distribution depends on:

- route
- tissue perfusion
- receptor binding
- dose
- proteolysis

clearance.

Again:

PHARMACOLOGY IS NOT A MEME.

IGF-1 DES AND ORGAN GROWTH

Any systemic IGF1R agonism raises questions about:

- organ trophism
- cardiac tissue
- bowel
- soft-tissue growth
- kidney

spleen.

The fact that DES may act particularly strongly in:

- IGFBP-rich tissue

makes:

TISSUE-SPECIFIC GROWTH PATTERNS

especially important to study.

Again:

ANABOLIC SIGNAL $\neq$ MUSCLE-SELECTIVE SIGNAL.

IGF-1 DES AND CARDIAC PHYSIOLOGY

IGF1R signaling can:

- support cardiomyocyte survival
- influence hypertrophy

affect metabolic function.

But:

- adaptive signaling

and:

- pathological remodeling

are different outcomes.

Again:

MORE CARDIAC GROWTH SIGNAL IS NOT AUTOMATICALLY CARDIOPROTECTION.

IGF-1 DES AND KIDNEY

IGF signaling can influence:

- renal growth
- filtration

tubular function.

If systemic DES strongly engages IGF1R:

renal physiology cannot simply be ignored.

Again:

A GROWTH FACTOR REACHES ORGANS TOO.

IGF-1 DES AND BONE

IGF-1 is central to:

BONE GROWTH AND REMODELING.

DES therefore has mechanistic relevance to:

osteoblast and skeletal signaling.

But:

direct DES-specific human fracture or osteoporosis data are not established.

Again:

BONE PATHWAY INVOLVEMENT $\neq$ BONE THERAPY.

IGF-1 DES AND CARTILAGE

IGF signaling is strongly anabolic for:

CHONDROCYTES.

Potential effects include:

- proteoglycan synthesis
- matrix formation.

But osteoarthritis involves:

- | | |
|----------------------|----------------|
| • matrix degradation | • inflammation |
| • subchondral bone | • mechanics |

senescence.

Again:

ANABOLIC MATRIX SIGNAL $\neq$ JOINT REGENERATION.

IGF-1 DES AND TENDON

IGF signaling can influence:

- collagen synthesis
- fibroblast activity

connective-tissue metabolism.

But:

there is not strong evidence that systemic or local DES administration:

RESTORES HUMAN TENDON STRUCTURE AND FUNCTION.

Again:

COLLAGEN SIGNALING $\neq$ TENDON HEALING PROOF.

IGF-1 DES AND “SITE GROWTH”

This deserves another explicit warning because the claim is so common.

The logic:

inject DES into muscle



muscle grows locally.

But to demonstrate true site-specific hypertrophy you would need:

- | | |
|--------------------------------|--------------------------------|
| • controlled human study | • matched contralateral muscle |
| • imaging | • standardized training |
| • systemic hormone measurement | |

tissue pharmacokinetics.

That evidence is not robustly established.

Again:

MECHANISTIC POSSIBILITY $\neq$ VERIFIED LOCAL HYPERTROPHY PROTOCOL.

THE MUSCLE-LOCALIZATION PROBLEM

If the goal is true muscle targeting:

future drug development should focus on:

- muscle-specific receptor targeting
- local depot technology
- antibody conjugates
- tissue-responsive prodrugs
- gene delivery

engineered extracellular-matrix binding.

Again:

TRUE TARGETING IS A DELIVERY PROBLEM - NOT SIMPLY AN INJECTION-SITE PROBLEM.

IGF-1 DES AND PERFORMANCE

There is no strong controlled human evidence establishing DES as a therapy that reliably improves:

- strength
- power
- sprint performance
- endurance

recovery time.

Again:

MYOGENIC SIGNALING $\neq$ ATHLETIC PERFORMANCE.

MUSCLE MASS $\neq$ STRENGTH

Even if hypertrophy occurs:

strength depends on:

- neural recruitment
- fiber architecture
- tendon
- technique

muscle quality.

Again:

ANATOMY $\neq$ FUNCTION.

IGF-1 DES AND RECOVERY

The mechanism is certainly relevant.

IGF1R supports:

- cell survival
- protein synthesis
- myogenesis

connective-tissue signaling.

But broad claims like:

FASTER RECOVERY

remain too vague.

Recovery from:

muscle damage?

tendon injury?

surgery?

nerve injury?

overtraining?

These are:

DIFFERENT BIOLOGIES.

Again:

DEFINE THE INJURY BEFORE DEFINING THE PEPTIDE.

IGF-1 DES AND NEUROREGENERATION

Neural-cell models show strong responsiveness to:

DES.

That makes neuroregeneration biologically interesting.

But:

human nerve repair involves:

- Schwann cells
- target reinnervation
- immune clearing
- axonal transport
- extracellular matrix

rehabilitation.

Again:

NEUROTROPHIC SIGNAL $\neq$ FUNCTIONAL REINNERVATION.

IGF-1 DES AND LONGEVITY

Just as with LR3:

it would be biologically simplistic to call:

IGF-1 DES AN ANTI-AGING PEPTIDE.

IGF signaling is anabolic.

But:

reduced insulin/IGF signaling is associated with lifespan extension in multiple experimental organisms.

Again:

GROWTH + LONGEVITY CAN PULL IN DIFFERENT DIRECTIONS.

THE ANABOLISM-MAINTENANCE TRADEOFF

High growth signaling:

- protein synthesis
- proliferation
- hypertrophy

Low-growth signaling environments may favor:

- autophagy
- stress resistance

cellular maintenance.

Again:

MAXIMUM ANABOLISM $\neq$ MAXIMUM HEALTHSPAN.

IGF-1 DES AND AUTOPHAGY

AKT $\rightarrow$ mTOR signaling can suppress:

AUTOPHAGIC PROGRAMS.

That may be useful during:

growth.

But chronic excessive mTOR activity may have:

different consequences.

Again:

THE SIGNAL THAT BUILDS CAN ALSO SUPPRESS THE SIGNAL THAT CLEANS.

This is another reason:

duration and context matter.

DES AND INSULIN SIGNALING

IGF1R and insulin receptors share:

- structural homology
- IRS proteins

PI3K

AKT.

Therefore:

changing IGF1R exposure can influence:

THE SAME METABOLIC SIGNALING NETWORKS USED BY INSULIN.

Again:

GROWTH AND METABOLISM ARE INTERCONNECTED.

THE HYBRID-RECEPTOR QUESTION

Cells can express:

IGF1R / INSULIN-RECEPTOR HYBRIDS.

These hybrid receptors may respond to:

IGF ligands.

At high pharmacologic exposures:

hybrid-receptor signaling could become increasingly relevant.

Again:

RECEPTOR NETWORK $\neq$ SINGLE RECEPTOR.

IGF-1 DES AND IGFBP FEEDBACK

Even if DES binds many IGFBPs poorly:

the cells can still change:

IGFBP EXPRESSION.

Neuroblastoma studies demonstrated that IGF signaling itself can increase certain IGFBPs, including IGFBP-6, as part of a:

NEGATIVE-FEEDBACK RESPONSE.

Again:

THE SYSTEM CAN BUILD A NEW BRAKE WHEN THE OLD BRAKE IS BYPASSED.

THE ADAPTIVE-BRAKE MODEL

DES → IGF1R signaling ↑ → cell responds → IGFBP expression ↑ → future IGF signaling restrained.

Even if DES resists some binding:

other IGFBP-mediated or receptor-level mechanisms may remain.

Again:

BIOLOGY RESISTS UNCHECKED SIGNALING THROUGH MULTIPLE LAYERS.

THIS IS WHY DES DOES NOT MEAN “UNREGULATED IGF”

Reduced IGFBP binding:

yes.

Completely unregulated:

no.

Other controls remain:

- | | |
|-----------------------------|-----------------------------|
| • receptor internalization | • receptor phosphatases |
| • IRS feedback | • mTOR/S6K feedback |
| • endogenous GH suppression | • IGFBP-independent actions |

ligand clearance.

Again:

ESCAPING ONE BRAKE DOES NOT REMOVE ALL BRAKES.

IGF-1 DES AND RECEPTOR DESENSITIZATION

Chronic IGF1R stimulation can potentially produce:

- receptor internalization
- downregulation

signaling adaptation.

How much this occurs with repeated DES exposure in humans is:

NOT WELL CHARACTERIZED.

Again:

ACUTE POTENCY $\neq$ CHRONIC POTENCY.

THE SIGNAL-DURATION QUESTION

- Brief high receptor signal

versus:

- longer moderate receptor signal

may produce:

different biology.

This parallels:

CJC-1295

vs:

- Modified GRF

but now at:

IGF1R.

Again:

TIME REMAINS PART OF THE MECHANISM EVEN AT THE FINAL GUIDE.

IGF-1 DES AND PRODUCT IDENTITY

This is especially important because:

DES is a:

67-AMINO-ACID DISULFIDE-BONDED PROTEIN.

It is much more structurally demanding than:

a simple pentapeptide.

Correct activity depends on:

- full sequence
- proper folding
- oxidation state
- disulfide bonding
- purity

concentration.

Again:

67 AMINO ACIDS ON A LABEL DO NOT GUARANTEE A CORRECTLY FOLDED BIOACTIVE GROWTH FACTOR.

DISULFIDE BONDS MATTER

IGF-1 family proteins contain:

INTRAMOLECULAR DISULFIDE BONDS.

If those bonds are incorrect:

the protein may:

- misfold
- lose receptor affinity

aggregate.

Again:

PEPTIDE IDENTITY INCLUDES THREE-DIMENSIONAL STRUCTURE.

This is particularly important for:

IGF analogs.

SEQUENCE $\neq$ FUNCTIONAL PROTEIN

A mass spectrometer could theoretically confirm:

correct molecular weight.

But:

that alone may not prove:

correct:

DISULFIDE CONNECTIVITY + BIOLOGICAL ACTIVITY.

Again:

CHEMICAL IDENTITY $\neq$ FUNCTIONAL CONFORMATION AUTOMATICALLY.

IGF-1 DES AND IMMUNOGENICITY

Any recombinant or synthetic protein analog can theoretically create:

- immune recognition

depending on:

- | | |
|--------------|--------------|
| • sequence | • aggregates |
| • impurities | • route |

repeated exposure.

The fact that DES resembles endogenous IGF-1 strongly may reduce some concerns.

But:

the truncation creates:

A NON-NATIVE TERMINUS.

Long-term human immunogenicity data remain:

LIMITED.

Again:

STRUCTURAL SIMILARITY $\neq$ ZERO IMMUNOLOGICAL RISK.

THE EVIDENCE LADDER

IGF-1 DES is a perfect final example.

DES EXISTS NATURALLY AS A TRUNCATED IGF FORM

YES.

IT LACKS THE FIRST THREE AMINO ACIDS

YES.

IT BINDS IGFBPS MUCH LESS STRONGLY

VERY STRONG.

IT RETAINS IGF1R AFFINITY

STRONG.

IT IS MORE POTENT THAN NATIVE IGF-1 IN MANY CELL SYSTEMS

YES.

IT CAN ENHANCE MYOGENESIS IN CULTURED MUSCLE CELLS

YES.

IT HAS ANABOLIC EFFECTS IN ANIMALS

YES.

IT SELECTIVELY BUILDS HUMAN SKELETAL MUSCLE

NOT ESTABLISHED.

IT IMPROVES HUMAN ATHLETIC PERFORMANCE

NOT ESTABLISHED.

IT REPAIRS HUMAN TENDON / CARTILAGE / NERVE

NOT ESTABLISHED.

IT IS A VALIDATED HUMAN ANTI-AGING INTERVENTION

NO.

Again:

THE EVIDENCE WEAKENS AS THE CLAIM MOVES AWAY FROM MOLECULAR BIOLOGY.

THE CORE MECHANISM MAP

NATIVE IGF-1

70 amino acids



N-terminal:

GLY-PRO-GLU



strong interaction with:

IGFBPs



transport

- buffering
- sequestration

controlled receptor availability.

Then:

post-translational / experimental truncation



remove residues:

1-3

DES(1-3)
IGF-1 - 67 aaIGFBP affinity
↓↓↓greater free /
accessible
ligand in
many local
environments

IGF1R

receptor
tyrosine
kinaseIRS → PI3K →
AKT → mTOR

- protein synthesis
- cell survival
- metabolism

and:

SHC → RAS → RAF → MEK → ERK

- proliferation
- growth

differentiation



potential effects in:

- skeletal muscle
- nervous tissue
- connective tissue
- other organs

- intestine
- bone
- kidney

tumor cells.

Meanwhile:

IGF1R signaling ↑



negative feedback



GH / endogenous IGF drive may ↓

and:

cells may increase:

OTHER REGULATORY BRAKES.

The core concept is:

IGF-1 DES DOES NOT CREATE A NEW GROWTH PATHWAY - IT REMOVES THE FIRST THREE AMINO ACIDS OF IGF-1, GREATLY WEAKENING BINDING-PROTEIN CONTROL WHILE PRESERVING IGF1R SIGNALING, THEREBY INCREASING LIGAND ACCESS TO THE RECEPTOR IN IGFBP-RICH ENVIRONMENTS.

WHAT THIS MECHANISM MAY SUGGEST

IGF-1 DES biology is relevant to research involving:

IGF1R	
<ul style="list-style-type: none">• IGFBPs• skeletal-muscle myogenesis• intestinal growth• growth-factor regulation• tissue repair biology• tumor biology	<ul style="list-style-type: none">• post-translational peptide processing• anabolic signaling• catabolic states• nervous-system growth• local growth-factor microenvironments• metabolic signaling

receptor vs binding-protein pharmacology.

Its strongest identity is:

A NATURALLY OCCURRING / EXPERIMENTALLY USED TRUNCATED IGF-1 VARIANT WITH PRESERVED IGF1R ACTIVITY AND MARKEDLY REDUCED IGFBP AFFINITY.

WHAT THIS MECHANISM DOES NOT PROVE

IGF-1 DES biology does not prove that:

<ul style="list-style-type: none">• DES is simply “stronger IGF-1”• DES is equivalent to mecasermin• DES is muscle selective• local injection guarantees site-specific hypertrophy• IGFBPs are merely obstacles• greater myogenesis in culture means human hypertrophy• gut trophic effects prove IBD treatment	<ul style="list-style-type: none">• DES is equivalent to native IGF-1• DES is equivalent to IGF-1 LR3• DES remains only at its injection site• reduced IGFBP binding is inherently superior physiology• greater cell proliferation means safer tissue repair• increased nitrogen retention proves athletic benefit• neuronal effects prove human nerve regeneration
<ul style="list-style-type: none">• cartilage IGF biology proves joint regeneration• greater anabolic signaling means better longevity• a serum IGF-1 measurement accurately reflects DES exposure• malignancy is irrelevant if the intended target is muscle	<ul style="list-style-type: none">• collagen signaling proves tendon repair• precise internet half-life values are established human pharmacokinetics• IGFBP-3 becomes irrelevant because DES binds it weakly• more IGF1R signal is always beneficial

every product labeled IGF-1 DES contains correctly folded active Des(1-3) IGF-1.

Again:

TRUNCATION + IGFBP ESCAPE + IGF1R SIGNALING + LOCAL MICROENVIRONMENT + SYSTEMIC DISTRIBUTION + FEEDBACK + GLUCOSE + PATIENT CONTEXT MATTER.

THE EVIDENCE, POTENTIAL APPLICATIONS, AND LIMITATIONS

MOLECULAR IDENTITY

VERY STRONG

Des(1-3) IGF-I is a:

67-AMINO-ACID TRUNCATED FORM OF IGF-I

lacking:

GLY-PRO-GLU

from the N-terminus.

NATURAL OCCURRENCE

MEANINGFUL BIOLOGICAL EVIDENCE

Des(1-3) IGF-I has been isolated from:

- bovine colostrum
- human brain
- porcine uterus

and likely arises through:

POST-TRANSLATIONAL CLEAVAGE.

REDUCED IGFBP AFFINITY

VERY STRONG

The first three residues are critically involved in:

IGFBP interaction.

Their deletion markedly decreases binding to multiple IGFBPs.

IGF1R AFFINITY

STRONG

Despite reduced IGFBP affinity:

DES retains approximately native-like affinity for:

IGF1R.

CELLULAR POTENCY

STRONG PRECLINICAL / CELLULAR EVIDENCE

DES can be approximately:

TENFOLD MORE POTENT

than native IGF-I in many cultured-cell hypertrophy / proliferation systems because IGFBPs restrain native IGF-I much more effectively.

MYOGENESIS

MEANINGFUL PRECLINICAL EVIDENCE

DES is more potent than native IGF-I in stimulating myogenic differentiation in skeletal-muscle-cell systems where local IGFBPs inhibit native IGF-I action.

ANABOLIC / NITROGEN METABOLISM

PRECLINICAL

Des(1-3) IGF-I demonstrated anabolic effects in nitrogen-restricted animals.

GUT TROPHIC BIOLOGY

MEANINGFUL PRECLINICAL EVIDENCE

Selective anabolic effects in gut tissues were prominent enough to motivate historical interest in catabolic and intestinal disease applications.

NEURAL / TUMOR CELL BIOLOGY

CELLULAR EVIDENCE

DES can stimulate proliferation and differentiation-related signaling in human neuroblastoma and colon-carcinoma cell models.

IGFBP-INDEPENDENT REGULATION

IMPORTANT MECHANISTIC EVIDENCE

IGFBP-3 can reduce IGF1R signaling even when DES is used, demonstrating that IGFBP biology extends beyond simple ligand sequestration.

DIRECT HUMAN THERAPEUTIC OUTCOMES

VERY LIMITED

There is no robust modern human clinical evidence establishing DES for:

- muscle hypertrophy
- cachexia
- tendon healing
- neuropathy
- sarcopenia
- inflammatory bowel disease
- cartilage regeneration

athletic performance.

HUMAN PHARMACOKINETICS

POORLY CHARACTERIZED

The exact pharmacokinetic profile frequently quoted in peptide circles is not supported by the same quality of human PK characterization available for established therapeutics.

ANTI-AGING / LONGEVITY

NOT ESTABLISHED

The IGF pathway has complex:

GROWTH VS LONGEVITY TRADEOFFS.

- Research

POST-TRANSLATIONAL PEPTIDE PROCESSING

This may be one of the most scientifically interesting uses of DES.

It demonstrates that:

the biological activity of a peptide can be changed simply by:

PROTEOLYTIC PROCESSING AFTER SYNTHESIS.

That deserves much more attention in peptide medicine.

IGFBP BIOLOGY

DES provides a tool for asking:

WHAT HAPPENS TO IGF SIGNALING WHEN LIGAND SEQUESTRATION BY IGFBPS IS GREATLY REDUCED?

That makes it:

A MOLECULAR PROBE OF IGF REGULATION.

MUSCLE

Future trials would need to measure:

- muscle cross-sectional area
- fiber type
- satellite cells

DEXA

MRI

- strength
- training adaptation

rather than simply:

serum IGF-1.

LOCAL DELIVERY

This remains a genuinely interesting pharmacology question.

Can DES be:

TRULY LOCALIZED

to a muscle or damaged tissue?

That would require:

- depot systems
- tissue-binding motifs
- controlled-release materials

receptor targeting.

Again:

TRUE LOCALIZATION REQUIRES DELIVERY ENGINEERING.

CATABOLIC STATES

Given its preclinical anabolic effects:

DES has historical relevance to:

- nitrogen restriction
- wasting

catabolism.

But the clinical question is:

CAN ANABOLIC BENEFIT BE ACHIEVED WITHOUT UNWANTED SYSTEMIC PROLIFERATIVE SIGNALING?

GUT BIOLOGY

DES may help clarify:

how IGFBPs regulate:

- intestinal renewal
- crypt proliferation

villus biology.

That could have research relevance to:

- short-bowel physiology
- mucosal injury

IBD.

But:

HUMAN THERAPEUTIC EVIDENCE IS NEEDED.

CANCER BIOLOGY

Because tumor cells can express:

IGF1R

and:

- IGFBPs,

DES is useful experimentally for separating:

IGF1R SIGNALING

from:

IGFBP SEQUESTRATION.

That is valuable mechanistic science.

NEUROBIOLOGY

The strong neuroblastoma-cell response shows:

that neural-lineage cells can respond powerfully to:

UNRESTRAINED IGF SIGNALING.

Future therapeutic research would need:

- neuron-specific targeting
- tumor exclusion

functional outcomes.

WHAT WE KNOW

IGF-1 DES - Des(1-3) IGF-I - is a 67-amino-acid truncated variant of native 70-amino-acid IGF-I.

It lacks the N-terminal Gly-Pro-Glu tripeptide.

Unlike IGF-1 LR3, which is an engineered 83-amino-acid analog, DES is a truncated form that has also been isolated naturally from biological tissues.

It has been identified in bovine colostrum, human brain, and porcine uterus, suggesting that proteolytic processing of native IGF-I can generate a biologically distinct endogenous variant.

That is a remarkable physiological idea:

THE BODY CAN CHANGE IGF SIGNALING BY CUTTING THREE AMINO ACIDS OFF THE PEPTIDE.

The major consequence is a dramatic reduction in IGF-binding-protein affinity.

Binding studies show that the N-terminal region of IGF-I is critical for interaction with multiple IGFBPs, while Des(1-3) IGF-I retains strong affinity for IGF1R.

This means:

RECEPTOR MESSAGE PRESERVED.

BINDING-PROTEIN RESTRAINT REDUCED.

That is why DES can appear far more potent than native IGF-I in many experimental systems.

A classic review described Des(1-3) IGF-I as approximately tenfold more potent than native IGF-I at stimulating hypertrophy and proliferation in cultured cells, largely because its reduced IGFBP affinity leaves more ligand available to reach IGF1R.

Again:

THE POTENCY DIFFERENCE IS ABOUT ACCESS, NOT SIMPLY A BETTER RECEPTOR.

Skeletal-muscle-cell studies provide a particularly clear example.

Muscle-derived IGFBPs can restrain native IGF-I-induced myogenesis, whereas DES largely escapes that inhibition and stimulates stronger differentiation-related responses.

This creates a strong:

MUSCLE MECHANISM.

But:

MUSCLE-CELL MECHANISM $\neq$ HUMAN MUSCLE-THERAPY EVIDENCE.

DES also demonstrates meaningful in-vivo anabolic biology.

Animal research showed anabolic effects during dietary nitrogen restriction, while review literature highlighted particularly prominent trophic effects in gut tissues.

That historical evidence generated interest in:

- catabolic states
intestinal disease.

But:

clinical evaluation remained much less developed.

DES also reveals that IGFBP biology is more complicated than simply binding the ligand.

IGFBP-3 can inhibit IGF1R signaling even when Des(1-3) IGF-I - which barely binds IGFBP-3 - is used as the ligand.

That means IGFBP-3 can regulate:

THE RECEPTOR ENVIRONMENT ITSELF.

Again:

ESCAPING THE BINDING PROTEIN DOES NOT ESCAPE EVERY FUNCTION OF THE BINDING PROTEIN.

This may be one of the most important mechanistic lessons in the entire IGF family.

Finally, DES has been used as an experimental probe precisely because its receptor affinity remains high while its IGFBP affinity is low.

Human brain and pituitary binding studies used DES and related low-IGFBP-affinity analogs to distinguish IGF1R sites from IGF-binding-protein sites.

Thus DES can be:

A PEPTIDE

and:

A PHYSIOLOGICAL TOOL FOR UNDERSTANDING THE SYSTEM.

WHAT WE THINK MAY BE HAPPENING

IGF-1 DES may be the perfect molecule to end the entire Peptide Guide library because it teaches:

THE SIGNAL IS NOT ONLY THE PEPTIDE.

The signal is:

PEPTIDE + BINDING PROTEINS + RECEPTOR + TISSUE + TIME.

Native IGF-1 enters the body.

But the body does not leave it free.

It surrounds the molecule with:

IGFBPS.

Those proteins determine:

where IGF goes.

how long it remains.

how much reaches the receptor.

Then:

three amino acids disappear.

Only:

GLY-PRO-GLU.

And suddenly:

the receptor still understands the message.

But:

the binding proteins lose much of their grip.

Now more ligand reaches:

IGF1R.

In muscle cells:

myogenesis becomes stronger.

In intestinal tissue:

trophic effects become stronger.

In neuronal / tumor-cell systems:

growth and differentiation signals change.

The peptide did not gain:

A NEW RECEPTOR.

It lost:

A REGULATORY INTERACTION.

That is an extraordinary distinction.

And it captures exactly what Praxis Peptide Institute should be teaching.

Because peptide medicine is not simply:

WHICH MOLECULE ACTIVATES WHICH RECEPTOR?

It is also:

WHAT RESTRAINS THE MOLECULE?

WHAT TRANSPORTS IT?

WHAT DEGRADES IT?

WHAT PROCESSES IT?

WHAT TISSUE SEES IT?

WHEN DOES THE SIGNAL STOP?

IGF-1 DES is:

LESS PEPTIDE

but potentially:

MORE SIGNAL.

That alone should destroy the idea that peptide medicine can be learned through:

MEMORIZING NAMES AND DOSAGES.

WHAT REMAINS CONTEXT-DEPENDENT

Important questions include:

Which human tissues naturally generate Des(1-3) IGF-I?

Which proteases remove the N-terminal GPE tripeptide?

Is DES production increased after injury?

Exercise?

inflammation?

fasting?

wound healing?

pregnancy?

tissue regeneration?

Is DES predominantly local rather than endocrine?

What concentrations occur naturally?

How quickly is endogenous DES cleared?

Does the liver generate DES?

Muscle?

gut?

brain?

uterus?

Which tissues contain the greatest DES-to-native-IGF ratio?

Is DES a true physiological signaling molecule or mostly a degradation / processing product?

Can its production be regulated?

Do IGFBP proteases also influence DES generation?

Is PAPP-A involved?

Which protease creates the GPE cleavage?

Does cleavage occur extracellularly?

intracellularly?

during secretion?

How much weaker is DES binding to each individual IGFBP?

IGFBP-1?

IGFBP-2?

IGFBP-3?

IGFBP-4?

IGFBP-5?

IGFBP-6?

Is the reduction uniform?

Does DES still interact meaningfully with certain IGFBPs at high concentrations?

How much IGFBP-independent regulation remains?

How important is IGFBP-3's receptor-level inhibitory action?

Does IGFBP-3 alter IGF1R conformation?

membrane environment?

internalization?

Can DES overcome IGFBP-3 inhibition at higher exposure?

Should it?

What is the exact affinity of DES for IGF1R compared with native IGF-I?

Does DES alter receptor activation kinetics?

Autophosphorylation duration?

receptor internalization?

receptor recycling?

IRS1 vs IRS2 recruitment?

PI3K vs MAPK balance?

Is DES signaling biased?

Does truncation alter receptor conformation?

Does DES activate insulin receptor-A?

insulin receptor-B?

hybrid receptors?

At what concentrations?

Does this contribute to glucose lowering?

What is the actual human hypoglycemia risk?
How does fasting change risk?
Does insulin co-exposure increase signaling?
Does exercise amplify muscle uptake?
Does postexercise hyperemia alter tissue distribution?
Does local injection meaningfully increase local tissue exposure?
For how long?
What fraction enters systemic circulation?
Is there true site-specific hypertrophy?
Can microdialysis measure local exposure?
Can stable-isotope techniques quantify local protein synthesis?
Does DES increase satellite-cell activation in humans?
Myonuclear accretion?
Fiber hypertrophy?
Does strength increase?
Which fiber types respond?
Type I?
Type II?
Does mechanical loading determine response?
Does DES without training meaningfully increase muscle?
Does protein availability determine benefit?
Does caloric deficit blunt it?
Could DES preserve lean mass during catabolism?
Does it improve nitrogen balance in humans?
Burns?
trauma?
severe illness?
cachexia?
Is the risk-benefit different in nonmalignant cachexia?
Does DES improve bowel mucosal mass in humans?
Could it help short bowel?
intestinal failure?
inflammatory bowel disease?
Does increased epithelial proliferation improve barrier function?
Or increase dysplasia risk in susceptible mucosa?
Could DES worsen neoplasia in chronically inflamed bowel?
Does IGF1R expression predict tissue response?
Does colon-cancer IGF1R biology create risk?
Which tumors are particularly IGF dependent?
Can DES stimulate occult tumor growth?
Does weak IGFBP binding increase tumor exposure?

Does IGFBP-3 still restrain tumor signaling independently?
Can tumor-specific IGFBPs change response?
Could DES promote differentiation rather than proliferation in certain tumors?
What determines which?
Does it alter apoptosis?
angiogenesis?
metabolic phenotype?
Does DES affect neuroblastoma differentiation in vivo?
Could controlled IGF signaling ever be therapeutically useful in neural disease?
Can neuron-specific delivery separate benefit from proliferation?
Does DES cross the blood-brain barrier?
At what concentration?
Does endogenous brain DES act paracrinally?
Does DES improve peripheral nerve regeneration?
Axonal growth?
Schwann-cell support?
Does functional reinnervation occur?
Does DES stimulate cartilage proteoglycan synthesis?
Can it improve cartilage repair?
Does systemic exposure increase unwanted bone growth?
Does DES change bone turnover?
osteoblasts?
osteoclasts?
Does it accelerate fracture healing?
Does it alter tendon collagen synthesis?
Does increased muscle growth outpace tendon adaptation?
Could that increase injury risk?
Does DES alter cardiac muscle?
Does it induce physiological or pathological hypertrophy?
Does it change renal mass or filtration?
Gut mass?
spleen?
pancreas?
Is tissue hypertrophy reversible?
What is the true human plasma half-life?
What is the tissue half-life?
How rapidly is DES proteolyzed?
Does renal clearance dominate?
Does weak IGFBP binding shorten vascular residence?
Could tissue residence still be prolonged despite rapid plasma clearance?
Is this why “short half-life but strong local potency” is discussed?

Can direct human microdialysis confirm that?
 Which assays detect DES?
 Do clinical IGF-1 immunoassays cross-react?
 Can LC-MS/MS distinguish native IGF-1 from DES?
 Can endogenous DES be measured clinically?
 Should it be?
 Does DES exposure suppress GH?

GHRH?

raise somatostatin?
 lower endogenous IGF-I?
 alter IGFBP-3?

ALS?

Does the axis rebound after discontinuation?
 Does chronic exposure downregulate IGF1R?
 How quickly?
 Does mTOR feedback create insulin resistance over time?
 Could acute glucose lowering transition into chronic metabolic dysregulation?
 What is the relationship between anabolic benefit and proliferative risk?
 Can receptor-biased IGF analogs favor AKT/mTOR over MAPK?
 Would that reduce mitogenic signaling?
 Can DES be modified further to target muscle?
 Could extracellular-matrix binding keep DES local?
 Could injury-responsive protease activation create a prodrug?
 Could a precursor release DES only at damaged tissue?
 Could endogenous GPE cleavage itself be harnessed therapeutically?
 Would modulating the protease that produces DES be safer than administering DES?
 Could PPI eventually classify IGF analogs not by name, but by:

- | | |
|-------------------------------------|--------------------|
| • receptor affinity | • IGFBP affinity |
| • insulin-receptor cross-reactivity | • tissue targeting |
| • half-life | • feedback effect |

anabolic-to-mitogenic ratio?

Again:

these are the questions needed to move from:

TRUNCATED IGF ANALOG

to:

PRECISION LOCAL GROWTH-FACTOR BIOLOGY.

THE PRAXIS LENS

DO NOT BEGIN WITH IGF-1 DES

Begin with:

WHY IS IGF1R SIGNALING BEING TARGETED, WHY IS THE NORMAL IGF-BINDING-PROTEIN SYSTEM BEING BYPASSED, IS LOCAL IGF AVAILABILITY ACTUALLY THE LIMITING NODE, AND WHAT OTHER TISSUES WILL RECEIVE THE SAME GROWTH SIGNAL?

Then:

PHYSIOLOGY

PATTERN



MECHANISM



EVIDENCE



RISK



MONITORING



DECISION

PHYSIOLOGY

Normal DES-relevant physiology includes:

GH

- native IGF-1
- post-translational cleavage
- locally produced IGF-1
- IGFBP-1 through IGFBP-6

IGFBP-3

ALS

- IGFBP proteases

IGF1R

- insulin receptors
- tissue-specific receptor expression
- nutrient state

mechanical loading.

DES changes:

THE N-TERMINAL REGULATORY INTERFACE OF IGF-1.

Again:

THREE RESIDUES CHANGE THE ENTIRE REGULATORY CONTEXT.

PATTERN

What is actually present?

true primary IGF deficiency?

muscle wasting?

sarcopenia?

malnutrition?

cachexia?

bowel injury?
nerve injury?
tissue repair failure?
active malignancy?
normal physiology with performance goals?

Again:

"MORE GROWTH" IS NOT A PHYSIOLOGICAL DIAGNOSIS.

MECHANISM

Does weak IGFBP binding actually solve:

THE BOTTLENECK?

If muscle is not growing because:

NO RESISTANCE TRAINING,

DES does not replace:
mechanical tension.

If tissue is not healing because:

POOR BLOOD FLOW,

more IGF1R signal may not fix:
ischemia.

If cachexia is driven by:

ACTIVE CANCER + INFLAMMATION,

- an anabolic signal may help one system while potentially stimulating another.

Again:

THE STRONGER THE SIGNAL, THE MORE IMPORTANT THE MECHANISTIC FIT.

EVIDENCE

Ask:

WHAT CLAIM ARE WE MAKING?

DES is 67-aa IGF-I lacking GPE?

VERY STRONG.

It occurs naturally in some tissues?

YES.

It binds IGFBPs much less strongly?

VERY STRONG.

It retains IGF1R affinity?

STRONG.

It is more potent in many cell systems?

YES.

It enhances myogenesis in cultured muscle cells?

YES.

It produces anabolic effects in animals?

YES.

Does it produce site-specific human muscle hypertrophy?

NOT ESTABLISHED.

Does it improve human athletic performance?

NOT ESTABLISHED.

Does it treat human IBD?

NOT ESTABLISHED.

Does it regenerate nerves?

NOT ESTABLISHED.

Does it improve longevity?

NOT ESTABLISHED.

Again:

KEEP THE CLAIM WHERE THE DATA ARE.

RISK

The central mechanistic concern is:

IGF1R SIGNALING WITH REDUCED NORMAL BINDING-PROTEIN BUFFERING.

Potential considerations include:

GLUCOSE

- hypoglycemic / insulin-like signaling

GROWTH

- unwanted tissue trophism
- organ effects
- soft-tissue growth

PROLIFERATION

- IGF1R activity in growth-sensitive or malignant tissue

AXIS FEEDBACK

- suppression of endogenous GH / IGF physiology

MONITORING LIMITATION

- uncertain assay recognition of the analog

PRODUCT

- correct 67-aa sequence
- correct folding
- disulfide structure

purity.

Again:

THE SIGNAL IS POWERFUL PRECISELY BECAUSE ONE LAYER OF PHYSIOLOGICAL RESTRAINT HAS BEEN REDUCED.

MONITORING

Monitoring should follow:

THE ACTUAL TARGET + THE SYSTEMIC GROWTH SIGNAL.

GLUCOSE

- fasting glucose
- symptom awareness
- CGM where clinically justified in a research setting

IGF SYSTEM

Potentially:

- native IGF-1

IGFBP-3

GH

but interpret carefully because:

THESE DO NOT DIRECTLY QUANTIFY DES EXPOSURE.

MUSCLE

if that is the hypothesis:

- MRI / ultrasound

DEXA

- strength
- function

standardized training response.

GUT

if that is the research target:

- nutritional absorption
- mucosal outcomes
- inflammatory markers

disease-specific endpoints.

WHOLE BODY

- unwanted growth
- edema
- organ-related symptoms

oncologic context.

Again:

IF THE GOAL IS LOCAL GROWTH, THE MONITORING MUST PROVE LOCAL BENEFIT WITHOUT UNACCEPTABLE SYSTEMIC GROWTH.

THE PRAXIS 5

MECHANISM

IGF-1 DES:

REMOVE GPE → IGFBP AFFINITY ↓ ↓ ↓ → IGF1R ACCESS ↑ → PI3K/AKT/mTOR + MAPK SIGNALING.

Its defining identity is:

TRUNCATION-DRIVEN IGFBP ESCAPE.

EVIDENCE

Natural occurrence:

MEANINGFUL.

Molecular identity:

VERY STRONG.

Reduced IGFBP affinity:

VERY STRONG.

IGF1R affinity:

STRONG.

Cellular potency:

STRONG.

Muscle-cell myogenesis:

MEANINGFUL PRECLINICAL.

Animal anabolic biology:

MEANINGFUL.

Human therapeutic outcomes:

VERY LIMITED.

Performance:

NOT ESTABLISHED.

Longevity:

NOT ESTABLISHED.

RISK

The biggest conceptual errors are:

1. ASSUMING "LOCAL" MEANS THE MOLECULE REMAINS AT THE INJECTION SITE.

2. ASSUMING REDUCED IGFBP BINDING MEANS IGFBPS NO LONGER MATTER.

3. ASSUMING MORE IGF1R SIGNAL MEANS SELECTIVE MUSCLE GROWTH.

4. ASSUMING CELLULAR POTENCY EQUALS HUMAN THERAPEUTIC VALUE.

Again:

LESS REGULATION $\neq$ MORE PRECISION.

Sometimes:

it means:

LESS PRECISION.

MONITORING

Do not rely solely on:

SERUM IGF-1.

The analog:

- may not be measured accurately
- may suppress endogenous production

may create tissue signaling without a proportional serum change.

Monitor:

THE TISSUE + FUNCTION + GLUCOSE + FEEDBACK + UNWANTED GROWTH.

Again:

THE PATIENT OUTCOME IS THE ASSAY THAT MATTERS MOST.

PATIENT CONTEXT

A patient with:

CATABOLIC MUSCLE LOSS

is different from:

a healthy athlete.

A patient with:

SEVERE BOWEL INJURY

is different from:

someone with normal GI physiology.

A patient with:

ACTIVE OR SUSPECTED MALIGNANCY

is different again.

A patient with:

PRIMARY IGF-1 DEFICIENCY

has an established native recombinant IGF-1 therapeutic pathway that should not simply be replaced conceptually with:

DES BECAUSE IT LOOKS MORE POTENT.

Again:

SAME RECEPTOR. DIFFERENT EVIDENCE. DIFFERENT CONTEXT.

SEVEN QUESTIONS TO ASK BEFORE IGF-1 DES

1. WHY IS DIRECT IGF1R STIMULATION BEING CONSIDERED?

Why not:

correct nutrition?

restore GH physiology?

use a validated IGF-1 therapy where appropriate?

address the local injury driver?

2. WHY REMOVE IGFBP CONTROL?

What exactly is the binding-protein system preventing that we actually want to overcome?

3. WHAT TISSUE IS THE TARGET?

skeletal muscle?

gut?

nerve?

bone?

connective tissue?

And:

WHAT ELSE WILL SEE THE SIGNAL?

4. IS "LOCAL" ACTUALLY LOCAL?

What evidence demonstrates:

tissue confinement?

5. WHAT IS THE MALIGNANCY / PROLIFERATION CONTEXT?

Because:

IGF1R is not:

A MUSCLE-SPECIFIC RECEPTOR.

6. HOW WILL THE SIGNAL BE MONITORED?

If standard IGF-1 assays do not accurately quantify:

DES,

what outcome demonstrates:

TRUE EXPOSURE + BENEFIT?

7. WHAT WOULD DEFINE SUCCESS?

Not:

“THE MOLECULE IS POTENT.”

Not:

“LEAN MASS WENT UP.”**But:**

THE SPECIFIC TARGET TISSUE IMPROVED IN A MEASURABLE FUNCTIONAL WAY - FOR EXAMPLE TRUE MUSCLE GROWTH WITH IMPROVED STRENGTH OR OBJECTIVE MUCOSAL RECOVERY - WHILE GLUCOSE, ENDOGENOUS GH-IGF FEEDBACK, ORGAN GROWTH, PROLIFERATIVE RISK, AND WHOLE-PATIENT PHYSIOLOGY REMAINED ACCEPTABLE.

KEY TAKEAWAYS

IGF-1 DES is a 67-amino-acid truncated form of human IGF-1 created by removal of the first three amino acids - Gly-Pro-Glu.

This is not merely an artificial bodybuilding peptide.

Des(1-3) IGF-I has been isolated naturally from bovine colostrum, human brain, and porcine uterus and is thought to arise through post-translational processing of native IGF-I.

That alone makes it biologically fascinating.

The first three amino acids are highly important for IGF-binding-protein interaction.

Removing them greatly decreases affinity for multiple IGFBPs while preserving strong IGF1R affinity.

This creates:

MORE RECEPTOR-ACCESSIBLE LIGAND

in environments where native IGF-I would otherwise be restrained.

That is why DES can be roughly tenfold more potent than native IGF-I in many cultured-cell hypertrophy and proliferation systems.

But:

MORE BIOLOGICAL POTENCY DOES NOT MEAN A BETTER RECEPTOR.

The difference is largely:

REDUCED IGFBP SEQUESTRATION.

Skeletal-muscle-cell research illustrates this clearly.

Muscle cells produce IGFBPs that inhibit native IGF-I-induced myogenesis, while DES largely escapes that inhibition and produces stronger differentiation-related responses.

That provides:

A REAL MUSCLE MECHANISM.

But:

CELLULAR MYOGENESIS ≠ VERIFIED HUMAN MUSCLE-BUILDING THERAPY.

DES also demonstrates meaningful preclinical anabolic and gut-trophic effects.

But the same growth-factor principle applies throughout the body.

IGF1R IS NOT A MUSCLE RECEPTOR.

It exists in:

- | | |
|---------------------|------------------|
| • gut | • nervous tissue |
| • bone | • kidney |
| • connective tissue | |

many tumor cells.

Human tumor-cell studies demonstrate that Des(1-3) IGF-I can strongly alter proliferation and differentiation-related biology.

That does not prove:

DES CAUSES CANCER.

It proves:

THE TARGET RECEPTOR EXISTS IN TISSUES OTHER THAN THE ONE YOU INTENDED TO GROW.

Perhaps the most sophisticated lesson comes from IGFBP-3.

Even though DES binds IGFBP-3 weakly:

IGFBP-3 can still reduce IGF1R activation through ligand-independent cellular mechanisms.

That means:

BYPASSING ONE TYPE OF REGULATION DOES NOT REMOVE THE REGULATORY SYSTEM.

That is systems biology.

IGF-1 DES should therefore not simply be classified as:

“THE SHORT-ACTING LOCAL MUSCLE IGF.”

A more accurate description is:

A TRUNCATED, LOW-IGFBP-AFFINITY IGF1R AGONIST THAT CAN PRODUCE ENHANCED LOCAL BIOLOGICAL ACTIVITY IN IGFBP-RICH TISSUES BUT WHOSE HUMAN DISTRIBUTION, PHARMACOKINETICS, THERAPEUTIC OUTCOMES, AND LONG-TERM SAFETY ARE FAR LESS CHARACTERIZED THAN ITS MOLECULAR AND PRECLINICAL BIOLOGY.

That distinction matters.

THE BOTTOM LINE

IGF-1 DES is the perfect final guide because it brings the entire PPI philosophy back to:

THE SYSTEM.

Start with:

IGF-1.

Seventy amino acids.

Powerful growth factor.

But the body does not simply leave IGF-1 free to activate receptors everywhere.

It surrounds it with:

BINDING PROTEINS.

Those proteins carry it.

Buffer it.

Sequester it.

Release it.

Shape where the signal can occur.

Then:

three amino acids disappear.

GLY.

PRO.

GLU.

Only three.

The receptor can still recognize the molecule.

But the binding proteins cannot hold it nearly as well.

Suddenly:

the same basic IGF message becomes:

MUCH MORE AVAILABLE.

Muscle cells respond more strongly.

Gut tissue responds.

Neural-lineage cells respond.

Tumor cells can respond.

And the biology teaches something very important:

THE POWER OF A PEPTIDE IS NOT DETERMINED ONLY BY THE RECEPTOR IT BINDS.

It is determined by:

THE ENTIRE REGULATORY ENVIRONMENT AROUND THAT RECEPTOR.

That includes:

binding proteins.
transport proteins.
proteases.
feedback loops.
tissue expression.
metabolic state.
signal duration.
And delivery.

That is why:

THREE MISSING AMINO ACIDS

can matter more than:

dozens of residues elsewhere.

And it is why peptide medicine cannot be learned by:
memorizing:

"DES = MUSCLE."

Because that throws away:

almost all the important biology.

The real questions are:

Why does the tissue need more IGF signaling?

Why are the binding proteins restraining the signal?

Is that restraint pathological?

Or protective?

Can the signal be kept local?

Does the target tissue actually lack anabolic signaling?

Will another tissue receive the same stimulus?

Will glucose fall?

Will endogenous GH suppress?

Will tumor cells respond?

Will the tissue actually function better?

Those are the questions that determine:

MEDICINE.

So the final Praxis question becomes:

"WHAT physiology is actually limiting tissue growth or repair, is inadequate local IGF1R activation truly the bottleneck, are IGF-binding proteins preventing a useful signal or performing an essential protective function, can Des(1-3) IGF-I increase the desired tissue response without creating unwanted systemic or proliferative signaling, and can that benefit

be demonstrated through objective function rather than inferred from the apparent potency of the molecule?”
That is the difference between:

CALLING IGF-1 DES A LOCAL MUSCLE-BUILDING PEPTIDE

and:

UNDERSTANDING HOW THREE AMINO ACIDS CAN CHANGE THE REGULATION OF AN ENTIRE GROWTH-FACTOR SYSTEM.

And that is exactly where this library should end:

NOT WITH A PEPTIDE NAME.

WITH A WAY OF THINKING.

PHYSIOLOGY → PATTERN → MECHANISM → EVIDENCE → RISK → MONITORING → DECISION

Because:

THE MOLECULE IS NEVER THE WHOLE STORY.

FINAL RECALL

ACCESS	CONTEXT	VERIFY
Three missing residues reduce IGFBP restraint	IGF1R exists far beyond the intended target	Prove functional benefit without unwanted systemic growth

STOP MEMORIZING PEPTIDES. START UNDERSTANDING THE SYSTEM.

Praxis Peptide Institute provides educational information and is not a substitute for individualized medical diagnosis or treatment. Des(1-3) IGF-I is a 67-amino-acid truncated IGF-1 variant lacking the N-terminal Gly-Pro-Glu sequence. It retains strong IGF1R activity while interacting much less strongly with normal IGF-binding proteins, producing enhanced biological activity in many experimental systems. Its strongest evidence concerns molecular pharmacology, IGFBP biology, cellular myogenesis, and preclinical anabolic and tissue-trophic effects. Direct human therapeutic, performance, regenerative, pharmacokinetic, and long-term safety data remain substantially less developed, and claims of strictly local muscle growth or precise short human half-life should not be treated as established without direct evidence.