CLINICAL LEARNING GUIDE

# Dihexa

PNB-0408 | Angiotensin IV Analog / HGF–c-Met System Modulator

*Mechanisms, Evidence, and Clinical Applications*

*Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education*

*For educational and research purposes only. Not medical advice. Dihexa is NOT FDA-approved for any indication; it is a research compound with NO human clinical trials, no IND/NDA, and no human pharmacokinetic data. Its two foundational mechanistic papers (Benoist 2014 and Kawas 2012) were RETRACTED, so the HGF/c-Met molecular target is unverified. The HGF/c-Met pathway it is proposed to enhance is a validated oncogenic pathway that multiple approved cancer drugs are designed to inhibit, and no carcinogenicity studies of Dihexa have been conducted. All use is investigational. Consult qualified healthcare providers before clinical use.*

## SECTION 1 · PROFILE OF THE PEPTIDE

### Overview

Dihexa (PNB-0408; N-hexanoic-Tyr-Ile-(6)-aminohexanoic amide; CAS 1401708-83-5; $C_{27}H_{44}N_4O_5$; MW 504.66 Da) is a synthetic oligopeptide developed as an analog of angiotensin IV (AngIV). Its standout pharmacological features are that it is orally active, blood-brain-barrier permeable, and metabolically stable — an unusual and genuinely attractive profile for a peptide aimed at the central nervous system. Across multiple rodent models it has shown potent pro-cognitive and synaptogenic effects.

Dihexa was originally characterized as an extraordinarily high-affinity (reported Kd ~65 pM) allosteric potentiator of hepatocyte growth factor (HGF) acting through the receptor tyrosine kinase c-Met. That framing now carries a major caveat: the two foundational mechanistic papers establishing the HGF/c-Met mechanism — Benoist 2014 (retracted April 2025, following a University of Washington review citing data falsification and inappropriate imaging) and Kawas 2012 (also retracted) — have been withdrawn. The reported binding affinity, allosteric mechanism, and HGF-antagonist blockade data from that work are therefore unverified, and the molecular target is no longer established.

Dr. Seeds is careful to separate two things. The retraction does not erase the observed benefits — the behavioral, cognitive, and synaptogenic findings rest on separate, unretracted papers — but it does reopen the question of how Dihexa works. His own view is that attention should shift back toward the angiotensin IV mechanism (Dihexa as an AngIV analog acting in the brain as an immune modulator, plausibly via inhibition of the IRAP enzyme), which could explain the CNS effects without invoking the oncogenic HGF/c-Met axis. He also frames the retraction as, in a sense, reassuring: because HGF/c-Met is a validated cancer-driving pathway, not building the case on chronic enhancement of it is, to him, a relief — while stressing that the cancer concern must still be kept squarely in mind.

Dihexa therefore occupies a singular position the practitioner must hold in full. It has impressive, reproducible, unretracted preclinical cognitive and synaptogenic data and a favorable oral/BBB profile — yet its proposed molecular target is now unverified, it has zero human data of any kind (no trials, no pharmacokinetics, no validated dose), and the pathway it is thought to engage is a documented oncogenic one with no carcinogenicity studies behind it. Promising preclinical signals are not the same as a verified mechanism or human safety, and that gap is the central thing to disclose.

## Compound Profile

| Property | Detail |
|---|---|
| Name | Dihexa (PNB-0408); N-hexanoic-Tyr-Ile-(6)-aminohexanoic amide |
| Identifiers | CAS 1401708-83-5; formula $C_{27}H_{44}N_4O_5$; MW 504.66 Da |
| Classification | Synthetic oligopeptide; angiotensin IV (AngIV) analog; proposed HGF/c-Met modulator |
| Key properties | Orally active; blood-brain-barrier permeable; metabolically stable |
| Proposed target | HGF/c-Met system (reported Kd ~65 pM) — NOW UNVERIFIED (source papers retracted); AngIV/IRAP mechanism proposed |
| Downstream (confirmed) | PI3K/AKT (wortmannin-reversible, in vivo); anti-inflammatory cytokine shift |
| Half-life (rat) | Serum ~335.5 min (~5.6 h) oral; estimated i.v. t½ ~12.68 d; i.p. t½ ~8.83 d |
| Routes (preclinical) | Oral (primary), i.p., i.c.v.; local hydrogel/IM in nerve-repair work |
| Human PK/dose | UNKNOWN — no human pharmacokinetics; no validated human dose |
| Regulatory | NOT FDA-approved; research compound only; no human trials, no IND/NDA |

## Where Dihexa Sits

Within the neuroprotection group, Dihexa is the cognition/synaptogenesis-oriented small oligopeptide — distinguished from the brain-derived hydrolysates (Cerebrolysin, Cortexin) by being a single defined molecule with a defined structure and an oral, BBB-permeable, metabolically stable profile. Its proposed biology connects it to two big systems: the HGF/c-Met growth-factor axis (now mechanistically in question) and the renin-angiotensin system via angiotensin IV. In practice Dr. Seeds describes it used for early cognitive concerns and for damping neuroinflammatory microglial activation (lowering TNF-α and IL-1β, raising IL-10), with additional preclinical interest in Parkinson's models, otoprotection, peripheral nerve repair, and stem-cell differentiation. As with the rest of this group, the breadth is the appeal — but here the mechanistic uncertainty and the oncogenic-pathway concern are unusually prominent.

> **⚠ Dihexa is NOT FDA-approved and has had ZERO human clinical trials — no human safety, efficacy, or pharmacokinetic data exist. Its two foundational HGF/c-Met mechanism papers (Benoist 2014, Kawas 2012) have been RETRACTED, so the molecular target is unverified. The HGF/c-Met pathway is a validated oncogenic pathway that approved cancer drugs (cabozantinib, crizotinib, capmatinib) are designed to INHIBIT; Dihexa is proposed to ENHANCE it, and NO carcinogenicity studies have been done. All use is investigational, and these facts must be disclosed plainly.**

# SECTION 2 · MODES OF ACTION AND MECHANISMS

Dihexa's mechanism must be discussed in two layers: a proposed primary mechanism that is now unverified because its source papers were retracted, and a set of downstream and behavioral findings that remain valid in separate, unretracted work. The honest summary is that Dihexa clearly does something pro-cognitive and synaptogenic in rodents, but exactly how it does it is again an open question.

## Proposed Primary Mechanism: HGF/c-Met (Now Unverified)

HGF is a multifunctional cytokine that signals through the receptor tyrosine kinase c-Met, a pathway important for neurogenesis, neuroprotection, and synaptic plasticity. Dihexa was characterized as an allosteric potentiator of HGF — facilitating HGF dimerization and augmenting c-Met phosphorylation at picomolar concentrations (reported Kd ~65 pM), with downstream activation of PI3K/AKT, Ras/MAPK, and STAT3 producing neuroprotection, synaptogenesis, anti-apoptosis, and anti-inflammation. Critically, the seminal source for this model (Benoist 2014) and the earlier AngIV-analog/HGF-binding paper (Kawas 2012) have both been retracted. The reported affinity, the allosteric-potentiation model, and the HGF-antagonist blockade data are therefore no longer verified, and whether Dihexa is an allosteric potentiator of HGF or an independent c-Met activator — or whether HGF/c-Met is the relevant target at all — is unresolved.

## The Angiotensin IV / IRAP Mechanism (Dr. Seeds' Preferred Framing)

Because the HGF/c-Met basis is now in doubt, Dr. Seeds points back to Dihexa's identity as an angiotensin IV analog. Within the renin-angiotensin system, AngIV acts in the brain less as a hemodynamic agent (the role of angiotensin II) and more as an immune modulator. Mechanistically, AngIV can inhibit the IRAP enzyme (insulin-regulated aminopeptidase), which normally degrades peptides such as somatostatin, vasopressin, the enkephalins, and oxytocin; by limiting that degradation, it shifts microglial activation, fostering a more anti-inflammatory environment with greater synaptic plasticity and neurogenesis. Dr. Seeds's read is that this AngIV/IRAP route — distinct from, and not oncogenic like, HGF/c-Met — is the more likely explanation for Dihexa's CNS effects and the direction future mechanistic work should take.

## Downstream Signaling (PI3K/AKT Confirmed In Vivo)

Whatever the upstream target, the PI3K/AKT downstream pathway is confirmed and functionally important: in APP/PS1 transgenic Alzheimer mice, the PI3K inhibitor wortmannin reversed all of Dihexa's effects, establishing PI3K/AKT dependence (Sun 2021, unretracted). Through this axis Dihexa is anti-apoptotic (cell-survival signaling) and anti-inflammatory — in the same model it decreased IL-1β and TNF-α and increased the anti-inflammatory cytokine IL-10, and reduced astrocyte and microglial activation. The Ras/MAPK and STAT3 arms are known to lie downstream of c-Met but, for Dihexa specifically, remain mechanistic inference rather than demonstrated fact.

## Synaptogenesis (The Strongest Unretracted Finding)

The most striking unretracted data are synaptogenic. In hippocampal neurons (McCoy 2013), Dihexa at $10^{-12}$ M produced roughly a 3-fold increase in dendritic spine density over five days (spines per 50 μm rising from ~15 to ~41), and even a brief 30-minute exposure increased spine number and spine-head width — indicating rapid structural plasticity. The new spines are functional: they are positive for VGLUT1, synapsin, and PSD-95, and AMPA-receptor mEPSC frequency and amplitude rose, confirming functional synapse formation. This synaptogenic activity is the clearest, best-supported piece of Dihexa's mechanism and is independent of the retracted HGF/c-Met work.

> **Key mechanistic point: Dihexa is an orally active, BBB-permeable angiotensin IV analog with potent, unretracted preclinical synaptogenic and pro-cognitive effects and confirmed, wortmannin-reversible PI3K/AKT signaling with an anti-inflammatory cytokine shift. But its proposed primary target, HGF/c-Met allosteric potentiation, is UNVERIFIED because the two foundational papers were retracted. Dr. Seeds suggests the angiotensin**

> **IV / IRAP mechanism is the more likely — and non-oncogenic — explanation. The effects are real in rodents; the molecular target is unresolved.**

### A Note on What the Retraction Does and Does Not Change

It is worth being precise about the retraction's scope. What is lost: the molecular-target story — the picomolar HGF binding, the allosteric-potentiation model, and the HGF-antagonist blockade data (Benoist 2014, Kawas 2012). What remains valid: the behavioral and cognitive rescue in the scopolamine model and the hippocampal synaptogenesis (McCoy 2013), and the APP/PS1 cognitive rescue with PI3K/AKT dependence and the anti-inflammatory cytokine profile (Sun 2021). In other words, the observations that Dihexa improves cognition and builds functional synapses in rodents stand; the explanation of how it engages its first molecular step does not. That is the honest state of the evidence, and it is why Dr. Seeds treats the mechanism as genuinely open.

## SECTION 3 · POINTS OF CLINICAL RELEVANCE

- **The defining tension.** Impressive preclinical data, an unverified mechanism, and zero human evidence.

Dihexa produces potent, reproducible pro-cognitive and synaptogenic effects across multiple rodent models — and these specific findings are unretracted. But its proposed molecular target rests on two retracted papers, and there are no human clinical trials, no human pharmacokinetics, and no validated human dose. Promising rodent data with an unverified mechanism and no human evidence is exactly the situation that demands caution and full disclosure.

- **The retraction reframes the mechanism, not the benefits.** How it works is open; that it does something in rodents is not.

Dr. Seeds's key interpretive point: the retracted work concerned the HGF/c-Met molecular target, while the behavioral, cognitive, and synaptogenic benefits come from separate, valid papers. His view is that the angiotensin IV / IRAP mechanism — Dihexa acting as a brain immune modulator — is the more likely and more promising direction, and that the field should look there rather than continuing down the HGF/c-Met path.

- **The oncogenic concern is real and central.** Dihexa enhances a pathway approved cancer drugs are built to inhibit.

HGF/c-Met activation promotes cell proliferation, tissue invasion, metastasis, angiogenesis, and apoptosis resistance — which is why cabozantinib, crizotinib, and capmatinib were developed to inhibit it. Dihexa, as originally characterized, enhances the same pathway, and no carcinogenicity studies have been done. Dr. Seeds suspects Dihexa's effect may be modulatory rather than pro-tumorigenic (and views the retraction of the HGF/c-Met basis as somewhat reassuring), but he is explicit that the cancer risk must be kept in mind until there is data.

- **A genuinely favorable pharmacology.** Oral, BBB-permeable, and metabolically stable — a real advantage.

Unlike most peptides in this group, Dihexa is orally active and crosses the blood-brain barrier, with confirmed oral bioavailability in rodents and a long apparent half-life. A systematic review highlighted it as the most promising AngIV analog for future cognitive testing specifically because of this metabolic stability, oral activity, and potency. This profile is the main reason it remains of interest despite the mechanistic uncertainty.

- **Potent synaptogenesis is the standout.** It builds functional synapses, fast, at picomolar concentrations.

The hippocampal-spine data (a ~3-fold increase in spine density, functional new synapses, rapid structural plasticity within 30 minutes) are the clearest, best-supported part of Dihexa's story and are unretracted. This is the kind of effect that would plausibly underlie a cognitive benefit if it translates.

- **Broad "beyond cognition" signals.** Otoprotection, nerve repair, and hepatocyte differentiation.

Preclinical work shows hair-cell protection against aminoglycoside ototoxicity (zebrafish), improved motor recovery in a rat sciatic-nerve-repair model combined with mesenchymal stem cells (with a reported 7-fold greater neurotrophic activity than BDNF), and growth-factor-free differentiation of human pluripotent stem cells into hepatocyte-like cells in vitro. These hint at broad therapeutic potential but are early, often single-study, and in some cases combination-dependent.

- **No human anything.** No trials, no PK, no validated dose, no long-term or carcinogenicity data.

This bears repeating as its own point: there is no human safety, efficacy, pharmacokinetic, long-term, or carcinogenicity data for Dihexa. Any human use is fully investigational and unsupported by human evidence.

## SECTION 4 · GENERAL DOSING INSTRUCTIONS AND DELIVERY OPTIONS

> **There is NO validated human dosing for Dihexa and NO human pharmacokinetic data. Every figure below is from rodent studies or is an extrapolation, NOT a validated human dose. Dihexa is NOT FDA-approved and has never been tested in humans. Do not use preclinical doses to make clinical dosing decisions.**

### Preclinical Dosing (Rodent — All Extrapolated)

| Route | Dose | Model | Outcome |
|---|---|---|---|
| Oral | 2.0 mg/kg/day | Scopolamine rat (acute) | Morris Water Maze deficit reversed ($p<0.001$) |
| Oral | 2.0 mg/kg/day | Aged rat (24 months) | Improved MWM on most test days (variable) |
| Oral | 1.44–2.88 mg/kg/day | APP/PS1 mouse (3 months) | Rescued spatial learning and memory |
| i.p. | 0.5 mg/kg/day | Scopolamine rat (acute) | Deficit reversed ($p<0.001$) |
| i.c.v. | 0.1–1.0 nmol | Scopolamine rat (acute) | Deficit reversed ($p<0.001$) |

### Pharmacokinetic Profile (Rat Only)

- Oral bioavailability: confirmed (effective in oral rodent studies).
- BBB penetration: confirmed ([3H]-dihexa vs [14C]-inulin distribution study).
- Serum half-life: ~335.5 min (~5.6 h) after oral dosing in rat.

- Estimated half-life by route: ~12.68 days i.v. and ~8.83 days i.p. (long-circulating in rat models).
- Human pharmacokinetics: UNKNOWN — no human data; rat-to-human extrapolation is unvalidated.

### Administration & Cycling in Practice (Convention, Not Validated)

- The extrapolated human dose used in practice has been roughly 20 mg/day orally — derived from rodent data, not pharmacokinetically validated.
- Oral is the practical route; some transdermal use has occurred historically, but practice has converged on oral dosing.
- Cycling described in practice: daily dosing with rotation — e.g., approximately three months on, then six weeks off, then back on — with the targeted use being early cognitive concerns and damping of neuroinflammatory microglial activation.
- Document baseline and follow-up cognitive status and inflammatory markers, and follow standard labs (renal/hepatic); no LFT changes have been observed in practice, though all such observations are anecdotal.

### Research Combinations (Not Clinical Protocols)

In preclinical work Dihexa has been combined with mesenchymal stem cells for peripheral nerve repair, with dexamethasone for growth-factor-free hepatocyte differentiation in vitro, and studied alongside aminoglycoside antibiotics in otoprotection models. These are research contexts, not validated clinical combinations, and the MSC nerve-repair work in particular makes Dihexa-specific attribution difficult.

## SECTION 5 · EVIDENCE PROFILE

### Preclinical Cognitive Evidence

| Study / Model | Design | Key Finding | Status |
|---|---|---|---|
| McCoy 2013 — scopolamine rat | Animal | MWM deficit reversed by oral/i.p./i.c.v.; oral = control level | Unretracted |
| McCoy 2013 — aged rat (24 mo) | Animal | Significant MWM improvement (with variability) | Unretracted |
| McCoy 2013 — hippocampal culture | In vitro | ~3-fold spine density; functional synapses; AMPA mEPSC up | Unretracted |
| Sun 2021 — APP/PS1 mouse | Animal | Cognition rescued; PI3K/AKT-dependent; anti-inflammatory shift | Unretracted |
| Ho & Nation 2018 | Systematic review | 8/9 studies: AngIV analogs aid memory; Dihexa “most promising” | Valid |

### Beyond Cognition (Preclinical)

- Otoprotection (Uribe 2015, zebrafish lateral line): Dihexa 1 μM protected hair cells from aminoglycoside (neomycin, gentamicin) ototoxicity; it did not block drug uptake but acted via intracellular survival signaling (HGF-dependent, blocked by a 6-AH antagonist; Akt/TOR/MEK partially involved). Preclinical only.

- Peripheral nerve repair (Weiss 2021, rat sciatic-nerve transection-repair): Dihexa 2–4 mg/kg via hydrogel, i.p., and IM combined with mesenchymal stem cells improved motor recovery and reduced foot-flexion contractures; reported ~7-fold greater neurotrophic activity than BDNF. Single study; combination design limits attribution.
- Hepatocyte differentiation (Siller 2015; Mathapati 2016, in vitro): Dihexa 100 nM + dexamethasone 100 nM differentiated human pluripotent stem cells into hepatocyte-like cells without exogenous protein growth factors — a potential cost-saving approach for regenerative medicine. In vitro only.

## Mechanistic Checklist (Evidence-Tiered)

| Item | Status | Source / Note |
|---|---|---|
| Synaptogenesis (hippocampal spines) | Confirmed | McCoy 2013 (unretracted) |
| Cognitive rescue (scopolamine model) | Confirmed | McCoy 2013 (unretracted) |
| Cognitive rescue (APP/PS1 model) | Confirmed | Sun 2021 (unretracted) |
| PI3K/AKT activation (wortmannin-reversible) | Confirmed | Sun 2021 (unretracted) |
| Anti-inflammatory cytokine profile | Confirmed | Sun 2021 (unretracted) |
| BBB penetration | Confirmed | McCoy 2013 (unretracted) |
| HGF/c-Met mechanism / molecular target | Unconfirmed | Primary papers RETRACTED (Benoist 2014, Kawas 2012) |
| Human cognitive efficacy | Unconfirmed | No human trials conducted |
| Long-term safety / carcinogenicity | Unconfirmed | Not studied |
| Human pharmacokinetics / optimal dose | Unconfirmed | Unknown |

## What Can and Cannot Be Confirmed

| Can confirm | Cannot confirm |
|---|---|
| Structure, MW, oral activity, BBB penetration (rat) | The HGF/c-Met molecular target (source papers retracted) |
| Potent synaptogenesis and functional synapse formation in vitro | Whether Dihexa is an allosteric HGF potentiator or independent c-Met activator |
| Cognitive rescue in scopolamine and APP/PS1 rodent models | Any human efficacy or safety (no trials conducted) |
| PI3K/AKT dependence and anti-inflammatory cytokine shift | Human pharmacokinetics, optimal dose, durability of benefit |
| HGF/c-Met is a validated oncogenic pathway (general biology) | Whether chronic Dihexa use promotes tumorigenesis (no carcinogenicity data) |

## Critical Evidence Gaps

- Molecular target unverified — the two foundational HGF/c-Met mechanism papers are retracted.

- Zero human clinical trials — no human efficacy, safety, or pharmacokinetic data; no IND/NDA filed.
- No long-term safety and no carcinogenicity studies — a serious gap given the oncogenic pathway involved.
- No validated human dose; rodent-to-human translation is unvalidated and species HGF/brain biology differs.
- Durability of cognitive benefit after stopping is unstudied; allosteric-vs-direct mechanism unresolved.

# SECTION 6 · CLINICAL CONSIDERATIONS

## Regulatory Status

Dihexa is not FDA-approved for any indication. It is a research compound: no human clinical trials have been conducted, no IND or NDA has been filed, and there is no human safety, efficacy, or pharmacokinetic data. Any human use is fully investigational and falls outside any approved framework.

## Oncogenic Risk (A Primary Consideration)

Because the proposed mechanism enhances the HGF/c-Met pathway, oncologic risk is a central clinical consideration rather than a footnote. HGF/c-Met activation promotes cell proliferation, tissue invasion, metastasis, angiogenesis, and apoptosis resistance — and several FDA-approved anticancer drugs (cabozantinib, crizotinib, capmatinib) work precisely by inhibiting c-Met. Dihexa is proposed to do the opposite, and no carcinogenicity studies exist. Dr. Seeds's view is that Dihexa's effect may be modulatory rather than pro-tumorigenic, and that the retraction of the HGF/c-Met basis makes this less certain a concern than it once seemed — but until there is direct data, chronic enhancement of an oncogenic pathway is a risk that must be disclosed and weighed.

## Evidence Integrity (The Retraction)

Practitioners should understand the retraction directly: the two papers that established Dihexa's molecular mechanism (Benoist 2014, retracted April 2025 after a University of Washington review citing data falsification and inappropriate imaging; and Kawas 2012) have been withdrawn. The behavioral, synaptogenic, and PI3K/AKT data in other papers (McCoy 2013, Sun 2021) are not retracted and remain valid. The net effect is a compound with real preclinical effects but an unverified target — a meaningful caveat for any risk-benefit discussion.

## Safety Profile

There is no systematic human safety data. In practice Dr. Seeds reports no documented adverse effects with Dihexa — including no nausea, diarrhea, or abdominal effects — with some dizziness and headache noted, and no observed changes in liver function tests. These observations are anecdotal and uncontrolled and cannot substitute for human safety studies; the absence of reported harm in limited use is not evidence of long-term safety, particularly regarding carcinogenicity.

## Contraindications & Cautions (Prudential)

- Active malignancy or significant cancer history: avoid — a precautionary contraindication given enhancement of the HGF/c-Met oncogenic pathway and the absence of carcinogenicity data.

- Pregnancy and lactation: avoid — no safety data.
- General: no human safety, drug-interaction, or monitoring data; all use is investigational and warrants thorough informed consent.

### Monitoring

There are no validated human monitoring biomarkers for Dihexa. Reasonable practice mirrors the lecture: baseline and follow-up cognitive assessment and inflammatory markers for the targeted indication, plus standard labs (renal and hepatic function). Given the oncogenic-pathway concern, age- and risk-appropriate cancer screening and a low threshold for stopping are prudent, and route, dose, duration, indication, and response should be documented.

### Patient Selection & Practitioner Posture

In practice Dihexa is used — orally, investigationally — for early cognitive concerns and to dampen neuroinflammatory microglial activation, with preclinical interest extending to Parkinson's models, otoprotection, and nerve repair. The responsible posture mirrors the evidence: present the genuinely promising, unretracted preclinical cognitive/synaptogenic data and the favorable oral/BBB profile honestly alongside the unverified molecular target, the complete absence of human data, and the unstudied oncogenic-pathway risk. Avoid in anyone with malignancy concerns, obtain full informed consent that names the retraction and the cancer concern plainly, use conservative extrapolated dosing if at all, and document outcomes carefully.

## SECTION 7 · A FINAL NOTE

Dihexa is one of the most interesting — and most cautionary — agents in the neuroprotection group. It is a small, orally active, blood-brain-barrier-permeable, metabolically stable angiotensin IV analog with potent, reproducible, unretracted preclinical effects: it builds functional hippocampal synapses (roughly tripling spine density at picomolar concentrations), rescues cognition in scopolamine and APP/PS1 models, and works through a confirmed, wortmannin-reversible PI3K/AKT pathway with a clear anti-inflammatory cytokine shift. A systematic review singled it out as the most promising compound of its class. Its preclinical signals even extend beyond cognition to otoprotection, peripheral nerve repair, and growth-factor-free hepatocyte differentiation.

And yet the honest accounting is sobering and unusual. The two foundational papers that established Dihexa's HGF/c-Met molecular mechanism have been retracted — one for data falsification — so the target is unverified, and whether Dihexa even acts primarily through HGF/c-Met is now an open question. Dr. Seeds argues, plausibly, that the angiotensin IV / IRAP route is the more likely and more attractive mechanism, precisely because HGF/c-Met is a validated oncogenic pathway that approved cancer drugs are built to inhibit. There are no human clinical trials, no human pharmacokinetics, no validated dose, and no long-term or carcinogenicity data of any kind.

For the practitioner, the posture follows directly from that tension. Dihexa's preclinical promise is real and its pharmacology is attractive, but a retracted mechanism, an oncogenic pathway, and zero human evidence are a combination that calls for unusual restraint. Used at all, it should be used investigationally and conservatively — orally, with the extrapolated dose, avoiding anyone with cancer concerns, with full informed consent that names the retraction and the oncogenic risk plainly, and with careful documentation of cognitive, inflammatory, and safety outcomes. The most useful thing a practitioner can do is help build the human evidence base responsibly while keeping the cancer question front of mind.

**Bottom line: Dihexa (PNB-0408) is an orally active, BBB-permeable angiotensin IV analog with potent, UNRETRACTED preclinical synaptogenesis (~3-fold hippocampal spines), cognitive rescue (scopolamine and APP/PS1 models), confirmed PI3K/AKT signaling, and an anti-inflammatory cytokine shift — plus a favorable oral/stable profile and broad "beyond cognition" signals. BUT its proposed HGF/c-Met target is UNVERIFIED (two foundational papers RETRACTED, one for falsification), it ENHANCES a validated oncogenic pathway with NO carcinogenicity data, and it has ZERO human trials, PK, or validated dose. Dr. Seeds favors an angiotensin IV / IRAP mechanism and is relieved the HGF/c-Met basis is no longer load-bearing. Genuinely promising in rodents — but mechanistically unverified, oncologically unstudied, and entirely untested in humans. Investigational only, with cancer concern front and center.**

## Selected References & Source Note

This guide was prepared from the recorded SSRP lecture on Dihexa by William Seeds, MD, and the accompanying slide deck. The references below are reproduced from the lecture's bibliography; two foundational mechanistic papers (Benoist 2014 and Kawas 2012) have been RETRACTED, as noted, and the corresponding retraction notices are listed. Readers should consult the primary sources — and the retractions — directly.


1. McCoy AT et al. Evaluation of metabolically stabilized angiotensin IV analogs as procognitive/antidementia agents. J Pharmacol Exp Ther. 2013;344(1):141-154. PMID: 23055539. [Animal Study — unretracted]
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3. Sun X et al. AngIV-analog dihexa rescues cognitive impairment and recovers memory in the APP/PS1 mouse via the PI3K/AKT signaling pathway. Brain Sci. 2021;11(11):1487. PMID: 34827486. [Animal Study — unretracted]
4. Kawas LH et al. Development of angiotensin IV analogs as hepatocyte growth factor/Met modifiers. J Pharmacol Exp Ther. 2012;340(3):539-548. PMID: 22129598. [RETRACTED]
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7. Weiss JB et al. Stem cell, granulocyte-colony stimulating factor and/or Dihexa to promote limb function recovery in a rat sciatic nerve damage-repair model. Ann Med Surg (Lond). 2021;71:102917. PMID: 34703584. [Animal Study]
8. Ho JK & Nation DA. Cognitive benefits of angiotensin IV and angiotensin-(1-7): a systematic review of experimental studies. Neurosci Biobehav Rev. 2018;92:209-225. PMID: 29733881. [Systematic Review]
9. Harding JW, Wright JW. Small molecule activation of the neurotrophin hepatocyte growth factor to treat Alzheimer disease. Neuroimmunol Neuroinflammation. 2020;7:246-259. [Review]
10. Retraction Notice: Benoist CC et al. J Pharmacol Exp Ther. 2025;392(4):103567. PMID: 40312093. [Retraction — April 2025]
11. Retraction Notice: Kawas LH et al. J Pharmacol Exp Ther. PMID: 22129598. [Retraction]


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