Dihexa — Basic Review Questions

1. What is Dihexa, and where does it come from?

Answer: 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), part of the renin-angiotensin system. Its standout pharmacological features are that it is orally active, blood-brain-barrier permeable, and metabolically stable — an unusually attractive profile for a CNS-directed peptide — and it has shown potent pro-cognitive and synaptogenic effects across multiple rodent models. It was originally characterized as an extraordinarily high-affinity (reported Kd ~65 pM) allosteric potentiator of hepatocyte growth factor (HGF) acting through the c-Met receptor, but that mechanistic framing is now in question (see below). It is best understood as a research compound with promising preclinical data and an unverified molecular target.

2. What is the central tension a practitioner must understand about Dihexa?

Answer: Dihexa has impressive, reproducible, unretracted preclinical cognitive and synaptogenic data and a genuinely favorable oral/BBB-permeable/metabolically stable profile — yet its proposed molecular mechanism rests on two retracted papers, it has zero human data of any kind (no clinical trials, no pharmacokinetics, no validated dose), and the pathway it is thought to engage (HGF/c-Met) is a documented oncogenic pathway with no carcinogenicity studies behind it. Promising rodent data with an unverified mechanism and no human evidence is exactly the situation that demands restraint and full disclosure. That gap — between strong preclinical signals and the absence of a verified mechanism or any human safety data — is the single most important thing to convey.

3. What happened with the retractions, and what does the retraction change (and not change)?

Answer: The two foundational papers that established Dihexa's HGF/c-Met molecular mechanism were retracted: Benoist 2014 (retracted April 2025, after a University of Washington review citing data falsification and inappropriate imaging) and Kawas 2012 (the earlier AngIV-analog/HGF-binding paper). What is lost is the molecular-target story — the reported picomolar HGF binding, the allosteric-potentiation model, and the HGF-antagonist blockade data. What remains valid (unretracted) is the behavioral and cognitive rescue plus hippocampal synaptogenesis from McCoy 2013, and the APP/PS1 cognitive rescue with confirmed PI3K/AKT dependence and the anti-inflammatory cytokine profile from Sun 2021. In short: the observation that Dihexa improves cognition and builds functional synapses in rodents stands; the explanation of its first molecular step does not. Dr. Seeds treats the mechanism as genuinely open as a result.

4. How does Dihexa work, given that its proposed mechanism is now unverified?

Answer: The proposed primary mechanism — allosteric potentiation of HGF leading to c-Met phosphorylation and downstream PI3K/AKT, Ras/MAPK, and STAT3 signaling — is now unverified because its source papers were retracted, and whether Dihexa is even

acting through HGF/c-Met is unresolved. Dr. Seeds's preferred framing returns to Dihexa's identity as an angiotensin IV analog: in the brain, AngIV acts as an immune modulator and can inhibit the IRAP enzyme (which degrades peptides such as somatostatin, vasopressin, the enkephalins, and oxytocin); by limiting that degradation it shifts microglial activation toward a more anti-inflammatory, plasticity- and neurogenesis-promoting state. Downstream, the PI3K/AKT pathway is confirmed and functionally important — the PI3K inhibitor wortmannin reversed all of Dihexa's effects in APP/PS1 mice — and is the basis for its anti-apoptotic and anti-inflammatory (IL-1β and TNF-α down, IL-10 up) actions. The strongest unretracted finding is synaptogenesis: at 10^{-12} M it roughly tripled hippocampal dendritic spine density, forming functional synapses (VGLUT1+, synapsin+, PSD-95+; increased AMPA mEPSC).

5. What is the oncogenic concern, and how does Dr. Seeds weigh it?

Answer: HGF/c-Met is a validated oncogenic pathway — its 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, as originally characterized, enhances the same pathway, and no carcinogenicity studies have been conducted, so chronic enhancement of an oncogenic pathway is a real, unstudied risk. Dr. Seeds's view is that Dihexa's effect may be modulatory rather than pro-tumorigenic, and he frames the retraction of the HGF/c-Met basis as somewhat reassuring (the case no longer depends on driving that pathway, and the angiotensin IV / IRAP route is non-oncogenic). But he is explicit that until there is direct carcinogenicity data, the cancer concern must be kept front and center and disclosed — and that Dihexa should be avoided in anyone with malignancy concerns.

6. What does the preclinical evidence look like, including effects beyond cognition?

Answer: The cognitive evidence (rodent only) is consistent: in the scopolamine amnesia model, Dihexa reversed Morris Water Maze deficits by oral (2.0 mg/kg/day), i.p. (0.5 mg/kg/day), and i.c.v. (0.1–1.0 nmol) routes, with oral performance indistinguishable from non-scopolamine controls; in aged (24-month) rats it improved MWM performance (with variability); and in APP/PS1 transgenic Alzheimer mice, three months of oral dosing rescued spatial learning and memory, increased neuronal counts and synaptophysin, decreased astrocyte/microglial activation, and shifted cytokines anti-inflammatory — all PI3K/AKT-dependent. A systematic review (Ho & Nation 2018) found 8 of 9 studies showed AngIV analogs improved memory and singled out Dihexa as the most promising. Beyond cognition: it protected zebrafish hair cells from aminoglycoside ototoxicity (intracellular survival signaling, not blocked uptake); improved motor recovery in a rat sciatic-nerve-repair model combined with mesenchymal stem cells (reportedly ~7x the neurotrophic activity of BDNF); and, with dexamethasone, differentiated human pluripotent stem cells into hepatocyte-like cells without exogenous growth factors in vitro. These are early, often single-study, and sometimes combination-dependent.

7. How is Dihexa dosed, and what are the key caveats about dosing?

Answer: The key caveat is that there is no validated human dosing and no human pharmacokinetic data — every figure is from rodent studies or extrapolation, and Dihexa has never been tested in humans. Preclinical doses include oral 2.0 mg/kg/day (scopolamine and aged-rat models), oral 1.44–2.88 mg/kg/day (APP/PS1, 3 months), i.p. 0.5 mg/kg/day, and i.c.v. 0.1–1.0 nmol. Rat pharmacokinetics show confirmed oral bioavailability and BBB penetration, a serum half-life of ~5.6 hours after oral dosing, and long estimated half-lives by other routes (~12.68 days i.v., ~8.83 days i.p.); human PK is unknown. In practice, the extrapolated human dose has been roughly 20 mg/day orally (not pharmacokinetically validated), given daily with cycling (for example, about three months on, six weeks off, then back on), aimed at early cognitive concerns and damping neuroinflammatory microglial activation. Oral is the practical route; some transdermal use occurred historically. All of this is investigational, and preclinical doses should not drive clinical dosing decisions.

8. What is known about safety, and what should guide responsible use?

Answer: There is no systematic human safety data. In limited practice Dr. Seeds reports no documented adverse effects — including no nausea, diarrhea, or abdominal effects — with some dizziness and headache noted and no observed liver-function changes; these observations are anecdotal and uncontrolled and cannot substitute for human safety studies, and the absence of reported harm in limited use is not evidence of long-term safety, especially regarding carcinogenicity. Responsible use mirrors the evidence: present the genuinely promising, unretracted preclinical cognitive/synaptogenic data and the favorable oral/BBB profile honestly alongside the unverified molecular target (two retracted papers, one for falsification), the complete absence of human data, and the unstudied oncogenic-pathway risk. Avoid Dihexa in anyone with active malignancy or significant cancer history, and in pregnancy/lactation (no data); obtain thorough informed consent that names the retraction and the cancer concern plainly; use conservative extrapolated dosing if at all; monitor cognitive and inflammatory measures and standard labs, with age- and risk-appropriate cancer screening and a low threshold for stopping; and document outcomes carefully to help build the human evidence base responsibly.