## MOTS-c — Basic Review Questions

1. What is MOTS-c, what type of peptide is it, and what is its regulatory status?

Answer: MOTS-c is a 16-amino acid mitochondrial-derived peptide (MDP) — meaning it is encoded not in the cell's usual nuclear DNA but in the mitochondrial genome (the 12S rRNA gene). Discovered in 2015, it was the first peptide shown to be made from that gene and to act as a circulating hormone, sending metabolic signals to distant tissues. It belongs to the same mitochondrial-peptide family as humanin. It is not FDA-approved — it is an FDA Category 2 bulk substance (with compounding restricted), is prohibited in sport by WADA, and has no completed human clinical trials, so all human use is investigational.

2. How does MOTS-c work?

Answer: Its core action is to activate AMPK, the cell's master metabolic "energy sensor." It does this through a distinctive route — briefly inhibiting the folate cycle, which causes a molecule called AICAR to build up, and AICAR is a powerful natural AMPK activator. Switching on AMPK then turns on the same downstream regulators as exercise (SIRT1, PGC-1α), boosting mitochondrial production, fat-burning, and glucose uptake in muscle. MOTS-c also does something remarkable: under stress it travels from the mitochondria into the cell nucleus and helps switch on protective antioxidant genes — the first known example of a mitochondrial peptide directly regulating nuclear genes ("mitonuclear communication").

3. Why is MOTS-c described as an "exercise mimetic," and what is the "metabolically challenged" selectivity?

Answer: Because it switches on the very same signals (AMPK, SIRT1, PGC-1α) that physical exercise activates — and the body's own MOTS-c actually rises sharply in muscle during exercise and declines with age. So it mimics, and can amplify, the cellular effects of exercise. A key feature is that it appears to act mainly under metabolic stress: in animal studies it produced little effect in healthy, metabolically normal subjects but clear benefits in states like obesity, age-related insulin resistance, and inflammation. This fits its identity as a stress-response signal, and it means it is most rationally aimed at metabolically challenged patients rather than healthy people seeking enhancement.

4. What are the main effects seen in preclinical studies?

Answer: The strongest and most consistent are metabolic: improved insulin sensitivity and glucose uptake in muscle, and an anti-obesity effect driven by increased heat production (thermogenesis) rather than by eating less. Animal MOTS-c roughly doubled treadmill performance across all ages. Beyond metabolism, studies show liver protection in fatty-liver (NASH) models, anti-inflammatory and host-defense effects (it improved survival in MRSA-infected mice), and bone-protective effects after ovary removal. The recurring thread through all of these is AMPK activation as the central switch.

5. What is the state of the evidence?

Answer: This is the crucial caveat. The preclinical evidence is relatively strong and internally consistent — multiple independent animal and laboratory studies — but the human evidence is thin. There are no completed human randomized trials of MOTS-c itself; the human data is limited to observational/biomarker studies (for example, blood MOTS-c correlating with insulin resistance and blood-vessel function) and a 7-day Phase 1a safety study of a related analog. There is no established human dose and no long-term safety data, so the biological rationale is promising but unproven in people.

6. What practical cautions apply to MOTS-c?

Answer: Several. Because human long-term safety is unknown and it is an FDA Category 2 substance, use is investigational and requires honest informed consent. Product purity is a real concern — research-grade material can be only ~60% pure, so pharmaceutical-grade sourcing matters. A genetic variant (K14Q) common in some East Asian populations makes the peptide less potent and may blunt the response. Because MOTS-c activates AMPK, combining it with other AMPK activators (such as metformin) can add to the glucose-lowering effect and needs monitoring. As with similar agents, active cancer is a reason to avoid it, given conflicting signals and no human safety data. Finally, since it is an exercise-mimetic, pairing it with actual exercise is considered the key co-intervention.