Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

MOTS-c

Evidence Summary

MOTS-c promotes metabolic flexibility and insulin sensitivity. Endogenous levels decline with age. Supplementation may have rejuvenating effects, but effective clinical translation has been lacking thus far.

Neuroprotective Benefit: MOTS-c may have anti-inflammatory properties and promote cellular energetics, but is not BBB penetrant.

Aging and related health concerns: MOTS-c enhances metabolic flexibility, improves insulin sensitivity, and may act as an exercise mimetic. MOTS-c rejuvenates aging phenotypes in muscle in mice, but its translational potential is currently limited.

Safety: MOTS-c therapeutic safety has not been established. The analog CB4211 was safe in a short-term study, but persistent injection site reactions were common. MOTS-c may interact with other drugs that target AMPK.

Availability: Research use	**Dose**: Not established	**Chemical formula:** $C_{101}H_{152}N_{28}O_{22}S_2$ **MW**: 2174.6 g/mol **Sequence**: H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH
Half-life: N/A	**BBB**: Not penetrant	
Clinical trials: MOTS-c analog CB4211 was tested in in Phase 1a/1b (n=88).	**Observational studies**: Endogenous MOTS-c levels decline with age and in populations with metabolic dysfunction.	

What is it?

Mitochondrial ORF of the 12S ribosomal RNA type-c (MOTS-c) is a 16 amino acid mitochondrial derived peptide (MRWQEMGYIFYPRKLR) encoded by a short open reading frame within 12S rRNA located in the mitochondrial genome (mtDNA) [2]. It is involved in the regulation of cellular bioenergetic homeostasis. MOTS-c is translated within the cytosol using the standard genetic code. It acts as a metabolic regulator primarily through activation of the AMP-activated kinase (AMPK), leading to an increase in lipid metabolism and cellular glucose flux. **Skeletal muscle is the primary target organ of MOTS-c**, where it acts to improve metabolic flexibility. It is not currently available for therapeutic use, but is used illegally as a performance enhancing drug by athletes [6].

CB411 is a MOTS-c peptide analog developed by CohBar, which was tested in a Phase 1a/1b trial in healthy volunteers along with a cohort with obesity and fatty liver disease (NCT03998514). CohBar also developed mitochondrial derived peptide analog-based therapeutics that were tested in preclinical models of obesity, fibrotic disease, and cancer. However, clinical development of CB411 has been discontinued due to the dissolution of CohBar.
In the intervening time, other companies have not yet emerged to continue development on mitochondrial derived peptide analog-based therapeutics, which likely stems from the technical challenges of this approach.

Neuroprotective Benefit: MOTS-c may have anti-inflammatory properties and promote cellular energetics, but is not BBB penetrant.

Types of evidence:

- 2 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
The potential role of endogenous MOTS-c in the brain is unclear, but may play a role in regulating metabolism [2]. At a dose that improved physical capacity, peripherally administered (i.p.) MOTS-c had no effect on cognition in mice [4]. Due to its lack of BBB penetrance, peripherally administered MOTS-c is not considered a viable therapeutic for CNS disorders

Memory impairment: CENTRALLY ADMINISTERED MOTS-C REDUCES INFLAMMATION-BASED MEMORY PROBLEMS (Preclinical)
MOTS-c was found to protect against Aβ42 and LPS (inflammation)-induced memory impairment on the novel object recognition and object location recognition tasks in mice [7]. However, since MOTS-c is not BBB penetrant, benefits were only seen when it was administered centrally (intracerebroventricularly) or intranasally when coupled to a cell-penetrating carrier. The protective effects involve the activation of AMPK signaling and the inhibition of pro-inflammatory cytokines.

APOE4 interactions: Not known

Aging and related health concerns: MOTS-c enhances metabolic flexibility, improves insulin sensitivity, and may act as an exercise mimetic. MOTS-c rejuvenates aging phenotypes in muscle in mice, but its translational potential is currently limited.

Types of evidence:

- 14 Biomarker studies examining plasma MOTS-c levels

- 1 Phase 1b trial of CB4211 in fatty liver disease
- Numerous laboratory studies

Challenges: TECHNICAL CHALLENGES HAVE HINDERED CLINICAL TRANSLATION
Numerous biomarker studies find an association between MOTS-c levels and health outcomes, particularly with respect to metabolic health. Preclinical studies also find that exogenously administered MOTS-c can have rejuvenating effects. Despite these promising findings, clinical development of MOTS-c, and other mitochondrial-derived peptides, as a therapeutic, have stagnated. This likely stems from the current lack of reliable delivery systems. These mitochondrial peptides have low bioavailability, poor stability, and short half-lives [8]. Another challenge is directing them to the desired location in the body, as they have tendency to persist at the injection site. As a result, we have a limited understanding of the ability of MOTS-c and other mitochondrial-derived peptides to influence physiology.

Lifespan: MOTS-C MAY PROMOTE LONGEVITY
MOTS-c is hypothesized to be involved in the longevity of the Japanese. The polymorphism located in the MOTS-c encoding mtDNA, m.1382A>C, causes a Lys14Gln replacement in MOTS-c, and is predicted to have a functional effect [9]. This polymorphism is specific for the Northeast Asian population, and is part of the haplogroup D4b2, which is associated with exceptional longevity. Although this variant increases the circulating levels of MOTS-c, which would be generally expected to be beneficial, this increase appears to be a compensatory response for the reduced activity of this variant. More recent evidence now suggests that this variant has a detrimental effect in this population by reducing MOTS-c activity, and increasing the risk for type 2 diabetes [10]. While this variant is unlikely to underlie the exceptional longevity of the D4b2 haplotype, it does not rule out a role for MOTS-c in longevity in humans.
Mice treated with MOTS-c (15 mg/kg 3x/week) starting in old age (23.5 months) showed a trend toward increased lifespan [4]. They had a 6.4% increase in median lifespan (970 vs 912 days), and a 7% increase in maximum lifespan (1120 vs 1047 days) (Hazard ratio 0.654, P=0.05). Additional research is needed to confirm these results and determine if earlier intervention has a stronger effect.

Aging: MOTS-C DECLINES WITH AGE AND HAS METABOLICALLY REJUVENATING EFFECTS (Preclinical)
MOTS-c is primarily produced in skeletal muscle, and in young healthy men circulating plasma levels are correlated with skeletal muscle levels [3]. However, this association is lost with age, suggesting changes in the regulation and secretion of MOTS-c with age. **Circulating levels of MOTS-c tend to decline with age**, while skeletal muscle MOTS-c expression was found to be approximately 1.5-fold higher in middle

aged (45-55) and elderly (70-81) men relative to young (18-30) men [3]. The increase in the mitochondrial derived peptide MOTS-c is consistent with the age-related fast to slow muscle fiber transition, as slow fibers have higher mitochondrial density. In the older cohort**, higher MOTS-c levels were associated with improved muscle quality**, based on maximal leg-press load relative to thigh cross-sectional area. MOTS-c may protect against the weakening of muscle strength, as it was found to block myostatin, an inhibitor of myogenesis, in the skeletal muscle of mice [11]. Due to increases in metabolic and oxidative stressors, as well as declines in endogenous protective mechanisms, MOTS-c supplementation may have a higher impact in older individuals. In rodents, MOTS-c supplementation protects against aging-related metabolic dysfunction, but has only marginal effects on the metabolism of healthy young mice [3].

In the D-galactose-induced aging model, MOTS-c (10 mg/kg i.p.) protected against aging phenotypes in a variety of tissues. MOTS-c prevented aging-related reductions in skin elastin and collagen, and reduced markers of cellular stress in the intestine [12]. MOTS-c protected against lipid accumulations in subcutaneous tissue and the liver by reducing mitochondrial stress. MOTS-c improved mitochondrial status by activating mitochondrial fusion and mitophagy pathways, and boosting endogenous antioxidant pathways. MOTS-c has also been shown to be protective in naturally aged mice. Elderly (23.5-month-old) male mice treated with MOTS-c (15 mg/kg 3x/week) had improved physical capacity [4].

Type 2 Diabetes/Obesity/Metabolic Syndrome: MOTS-C ENHANCES METABOLISM
Insulin sensitive tissues, including skeletal muscle and fat, are primary sites of action for MOTS-c, where it drives metabolic homeostasis [2]. The induction of endogenous MOTS-c and/or capacity to induce protective metabolic adaptations is impaired in the context of metabolic disorders. Preclinical studies suggest that exogenous MOTS-c treatment may be able to restore metabolic homeostasis.

In response to metabolic stress, MOTS-c can translocate to the nucleus in an AMPK dependent manner and regulate gene expression. MOTS-c lacks a nuclear localization signal, but instead its translocation is dependent on residues in its hydrophobic core (8YIFY11) [13]. MOTS-c increases glucose uptake and clearance and beta oxidation of fatty acids. In HEK293, MOTS-c treatment altered the metabolite profile within 4 hours, which included a reduction in metabolites involved in purine metabolism and dipeptide metabolism, and an increase in metabolites involved in acylcarnitine metabolism and the methionine cycle [2]. These changes are consistent with regulation of the folate cycle, an effect that is also seen with other AMPK activating therapies, such as metformin. However, the effects and metabolite profile may

depend on the baseline metabolic status of the organism. In mice with diet induced obesity, MOTS-c (2.5 mg/kg i.p. 2x/day for 3 days) treatment stimulated the beta oxidation of fatty acids, but did not appear to impact the folate cycle [14]. The major metabolic effects were on the reduction of sphingolipid metabolism, monoacylglycerol metabolism, and dicarboxylate metabolism [14].

MOTS-c enhances metabolic flexibility allowing for increased utilization of carbohydrates and lipids depending on their availability [4]. The ability of MOTS-c to promote beta oxidation of fatty acids reduces lipid accumulation in tissues, and prevents the associated oxidative stress induced by excess lipids [2]. MOTS-c enhances the metabolism of skeletal muscle, and contributes to the 'browning' of white adipose tissue [1]. MOTS-c promotes metabolic adaptations to cold by driving brown fat thermogenesis and reducing lipid trafficking to the liver. MOTS-c may serve as a messenger, conveying information about metabolic stress between metabolic regulating POMC neurons in the hypothalamus and peripheral tissues, such as adipose tissue [15]. In mice, mild mitochondrial stress triggered the expression of MOTS-c in the hypothalamus and beneficial metabolic adaptations, including thermogenesis, in adipose tissue. MOTS-c expression in POMC neurons may also be influenced by leptin levels. Meanwhile, severe mitochondrial dysfunction/metabolic stress did not elicit these protective changes.

Plasma MOTS-c levels were found to be reduced in a cohort of obese children and adolescents relative to controls (472.61 ±22.83 vs 561.64 ±19.19 ng/mL, $P < 0.01$, n=97) [16]. The effect was driven by the obese males, as MOTS-c levels trended lower, but were not significantly different in obese females compared to controls. In the males, MOTS-c levels were inversely correlated with body mass index (BMI) ($r = -0.521$, $P < 0.001$, waist circumference ($r = -0.559$, $P < 0.001$), waist-to-hip ratio ($r = -0.314$, $P = 0.010$), fasting insulin level ($r = -0.379$, $P = 0.002$), homeostasis model assessment of insulin resistance (HOMA-IR) ($r = -0.380$, $P = 0.001$), and glycated hemoglobin (HbA1c) ($r = -0.271$, $P = 0.027$), indicating that those with more severe metabolic dysfunction had lower levels of MOTS-c.

Similarly, plasma MOTS-c levels were found to be lower in individuals with type 2 diabetes, such that those with worse glucose control (i.e., higher Hb1Ac levels) had the lowest levels of MOTS-c [5]. In a small cohort of adults (n=10), MOTS-c levels were only correlated with measures of insulin sensitivity, HOMA and the Matsuda index, in lean individuals, suggesting that the relationship between MOTS-c and metabolic status is altered with obesity [17]. The dampening of MOTS-c seen in the obese may stem from a downregulation following chronic glucose overload and associated mitochondrial damage. This then likely explains the relationship between MOTS-c levels and glycemic control, as elevated glucose

can induce oxidative stress which impairs mitochondria, thus lowering MOTS-c. Consistent with this, a meta-analysis including 602 participants from six case-control and one cross-sectional study, found that circulating MOTS-c levels were lower in patients with type 2 diabetes (SMD: - 0.89, 95% CI - 1.12 to - 0.65) [18]. Meanwhile, the relationship with obesity was more complex, as MOTS-c levels were higher in some obese participants. The study authors hypothesize that the compensatory increase in MOTS-c may stem from increased metabolic stress, but over time the metabolic adaptations that lead to diabetes also dampen the MOTS-c response.

MOTS-c levels were also found to be lower in patients with chronic kidney disease, which is associated with metabolic disturbances, in both the plasma (185 ± 70 vs. 435 ± 124 ng/mL, $P < 0.0001$) and skeletal muscle (3.7 ± 1.8 vs. 7.5 ± 3.3 ng/mL, $P < 0.001$) [19]. Higher MOTS-c levels were associated with lower body weight, circulating lipids, and oxidative stress, suggesting that it has a protective effect in this population. The m.1382A>C (K14Q) SNP (rs111033358) in MOTS-c alters its structure in a manner that reduces its activity, making it a less effective insulin sensitizer. This SNP is primarily found in individuals of East Asian descent, and East Asian men with this variant were found to be at higher risk for type 2 diabetes, especially in men with low levels of physical activity [10].

A prospective biomarker study including 74 diabetic patients with heart failure found that the antidiabetic agents SGLT2 inhibitors (e.g. empagliflozin and dapagliflozin) mitigated levels of nitrosative stress and increased serum levels of MOTS-c [20].

Preclinical studies show that exogenous MOTS-c supplementation can restore insulin sensitivity, enhance lipid utilization instead of storage, and promote weight loss in obese or otherwise metabolically challenged rodents. Male mice treated with MOTS-c (5 mg/kg i.p. for 7 days) had improved whole body insulin sensitivity, and their skeletal muscle had increased activation of Akt in response to insulin [2]. The muscle insulin sensitivity of middle-aged mice (12 months old) was restored to the levels seen in young mice (3 months old). In high-fat diet fed male mice, MOTS-c (0.5 mg/kg/day i.p. for 3 weeks) prevented weight gain, improved glucose homeostasis, and reduced the accumulation of lipids in the liver. MOTS-c did not impact food intake, but instead increased energy expenditure, as indicated by increased heat output. These mice had less fat accumulation due to increased carbohydrate usage, increased beta oxidation of fatty acids, and thus less fat storage. The metabolic effects stem from the activation of AMPK, a central mediator of energy homeostasis [21].

Similar restoration of insulin sensitivity was seen in a mouse model of diet induced obesity for the MOTS-c peptide analog, CB4211 [22]. In cell culture, CB4211 potentiated insulin mediated reduction of glucose in hepatic cells, and inhibition of lipolysis in adipocytes. CB4211 potentiated the effects of insulin, but did not impact these processes on its own.

MOTS-c regulation appears to be sex dependent, with **males exhibiting a greater disruption in MOTS-c in the context of metabolic disease**, relative to females [16]. The decline in MOTS-c may be blunted in pre-menopausal women due to the protective effects of estrogen, and its ability to promote mitochondrial biogenesis. The loss of this compensatory mechanism may contribute to the increase in fat accumulation and induction of insulin resistance that commonly accompanies menopause. In ovariectomized female mice, MOTS-c (5 mg/kg i.p. for 5 weeks) reduced fat accumulation in white adipose tissue and liver, while increasing brown fat activation and improving insulin sensitivity [23]. The increase in energy expenditure was attributed to the activation of AMPK.

Exercise mimetic: MOTS-C IS INDUCED BY EXERCISE AND MAY ENHANCE PERFORMANCE
MOTS-c is induced in the skeletal muscle in response to exercise and promotes metabolic adaptations to exercise-related stress.
Skeletal muscle MOTS-c levels were shown to increase 11.9-fold in response to an acute bout of exercise on a stationary bike in healthy young men (aged 24.5 ± 3.7 years, n=10), while circulating levels increased 1.6-fold, from approximately 125 pg/mL to approximately 190 pg/mL. MOTS-c levels remained elevated following a 4-hour rest in the muscle (18.9-fold) and in the plasma (1.5-fold) [4]. A small study in young adults (n=20) assessed the relationship between serum MOTS-c levels and muscle strength parameters during an exercise test [24]. Serum MOTS-c was positively correlated with the average power and force of the jumping, as well as overall muscle mass and leg muscle mass. Serum MOTS-c levels were related to the amount of skeletal muscle, particularly type-II fast-twitch muscle fibers, rather than to respiratory exercise capacity (i.e. endurance), as measured by VO_2 max. While endurance exercise is well-established to confer hormetic mitochondrial stress and adaptations, MOTS-c levels do not necessarily track well with measures of endurance in human studies. Indeed, median serum MOTS-c levels were found to be lower in professional athletes (n=75) (2.36 ng/mL; IQR 1.74 to 4.18) relative to controls (n=30) (3.89 ng/mL; IQR 3.1 to 4.88), and were lowest in high endurance athletes (2.22 ng/mL; IQR 1.54 to 3.94) [25]. This could be related to a shift in muscle fiber composition, as force and power stem from fast-twitch fibers, while endurance is related to slow-twitch fibers [24]. There is some evidence to suggest that while MOTS-c is robustly induced in both fiber types, MOTS-c tends to remain within slow-twitch fibers, thus circulating MOTS-c levels may not be reflective of tissue levels in individuals with a predominance of slow-twitch fibers [3; 9]. This may also contribute to the sex difference in the utility of circulating MOTS-c levels as an indicator of metabolic dysfunction, since women tend to have a higher percentage of slow-twitch fibers, while men tend to have a higher percentage of fast-twitch fibers.

In male mice, MOTS-c treatment regulated glucose and amino acid metabolism in skeletal muscle and induced gene expression driving adaptations to metabolic stress in myoblasts. MOTS-c treatment also enhanced physical capacity in both aged (23.5-month-old) and obese (high fat diet fed) mice [4]. On a treadmill running test, MOTS-c treatment enhanced performance in all tested groups, including young healthy, young high-fat diet fed, middle aged (12-month-old), and elderly (22-month-old) mice. The old mice ran 2-fold longer and 2.16-fold farther than their untreated counterparts. The effect is related to the metabolic reprogramming of the skeletal muscle which allows for greater metabolic flexibility. Based on these properties, MOTS-c is used as a performance enhancing drug by athletes, and an LC/MS method for detecting MOTS-c with a lower limit of detection of 100 pg/mL, four metabolites, and two oxidation products (oxidation of the 2 methionine residues m/z 548 and 552) has been developed in accordance with the World Anti-Doping Agency's International Standard for Laboratories [6]. The metabolites are MOTS-c (5–16) ([M + 4H]4+ at m/z 393), MOTS-c (4–16) ([M + 4H]4+ at m/z 425), MOTS-c (3–16) ([M + 4H]4+ at m/z 472) and MOTS-c (2–16) ([M + 5H]5+ at m/z 409).

Non-Alcoholic Fatty Liver Disease: CB4211 REDUCES LIPIDS IN LIVER IN MICE; EFFECTS IN HUMANS APPEAR TO BE MODEST

The MOTS-c peptide analog CB4211 (5 or 15 mg/kg i.p. for 21 days) reduced body weight and liver steatosis in a mouse model of diet induced obesity [26]. The specificity for fat loss was greater for CB4211 than for liraglutide. In the STAM™ mouse model of NAFLD, CB4211 (15 mg/kg i.p. BID for 21 days) reduced NAFLD activity score by 33% when administered starting at 6 weeks of age. CB4211 also reduced liver triglyceride levels, and plasma levels of the liver enzyme ALT.

CB4211 was tested in patients with NAFLD as part of a Phase 1a/1b trial (NCT03998514). The study included 20 obese participants with at least 10% liver fat, with 11 participants treated with 25 mg CB4211 via subcutaneous injection once daily and nine treated with placebo for 28 days. Topline results were released by CohBar in 2021 (Press release). The study met its primary outcome of safety and included exploratory endpoints related to liver function. Relative to placebo, levels of liver enzymes of ALT and AST were reduced with CB4211 treatment by 25% and 17%, respectively. However, the amount of liver fat reduction based on MRI-PDFF measures was comparable between the groups (-5.03% vs -4.88%). Since the study was relatively short and not adequately powered for these exploratory measures, it is difficult to assess whether there could be clinical utility with longer term use or a different dosing paradigm. Clinical development for CB4211 has been discontinued due to the dissolution of CohBar.

Osteoporosis: MOTS-C REDUCES BONE LOSS (Preclinical)
Preclinical studies suggest that MOTS-c promotes osteoblast proliferation, differentiation, and mineralization, while inhibiting osteoclast production [27].
In a mouse model of menopause-related bone loss (ovariectomy), female mice treated with MOTS-c (5 mg/kg/day i.p. for 12 weeks) had reduced bone loss [28]. The effect was related to the inhibition of bone absorbing osteoclast formation via activation of AMPK. AMPK inhibits RANKL, which is the primary mediator of osteoclast differentiation. In primary cell culture, MOTS-c induced osteogenesis and mineralization in bone marrow stromal cells via activation of FOXF1 and TGF-β signaling [29]. This suggests that MOTS-c may promote bone repair and strengthening. MOTS-c may also promote the synthesis of type I collagen synthesis, a primary bone matrix protein through the TGF-β/Smad pathway [27].

Cardiovascular disease: MOTS-C LEVELS ASSOCIATED WITH VASCULAR FUNCTION
Plasma MOTS-c levels were found to be correlated with microvascular (R^2 = 0.14, p = 0.01) and epicardial (R^2 = 0.13, p = 0.02) endothelial function, based on responsiveness to acetylcholine [30].
Correspondingly, individuals (n=40) with endothelial dysfunction have reduced plasma levels of MOTS-c (154.3 ± 29.8 vs 184.7 ± 37.9 pg/mL, p = 0.007). Patients with acute coronary syndrome (n=18) were found to have lower levels of plasma MOTS-c and PGC-1α relative to controls (n=20) [31]. Plasma levels of MOTS-c and PGC-1α were also lower in patients with aortic valve disease (n=17) relative to controls (n=22) [32].
In addition to promoting vascular responsiveness, MOTS-c has been shown to inhibit vascular calcification and myocardial remodeling. In male rats, MOTS-c (5 mg/kg i.p. for 4 days) reduced vitamin D and nicotine-induced vascular calcification, with a 55% reduction in calcium content [33].

Pulmonary disease: MOTS-c LEVELS ASSOCIATED WITH LUNG FUNCTION
Biomarker studies indicate that MOTS-c levels are reduced in individuals with reduced lung function. Compared to smokers with normal lung function (n=47) (764 ng/mL; IQR 604 to 906), median serum levels of MOTS-c were lower in patients with stable chronic obstructive pulmonary disease (COPD) (n=142) (622 ng/mL; IQR 482 to 848) [34]. Participants with MOTS-c levels below the median, had lower oxygen saturation and reduced walking distance capacity.
Serum MOTS-c levels were also inversely correlated with the severity of obstructive sleep apnea, such that those with low MOTS-c had more hypoxic events [35].

Neuropathic pain: MOTS-C INHIBITS INFLAMMATORY PAIN (Preclinical)

In a formalin-induced inflammatory pain models, MOTS-c treatment (50 mg/kg i.p.) showed anti-nociceptive effects in male mice [36]. The effects were mediated by the activation of AMPK, and the suppression of ERK, p38 MAPK, and JNK signaling in the spinal cord. MOTS-c treatment was associated with a reduction in circulating pro-inflammatory cytokines (TNFα, IL-1β, IL-6), and an increase in anti-inflammatory cytokines (IL-10). It is not known whether MOTS-c can impact established pain, or if it only inhibits the induction of inflammatory neuropathic pain.

Infection/Sepsis: MOTS-C PRETREATMENT ENHANCES SURVIVAL (Preclinical)
In mice infected with methicillin-resistant Staphylococcus aureus (MRSA), MOTS-c pretreatment of 20 mg/kg 4 hours prior to infection improved survival from 20% to 79%, while post-treatment of 50 mg/kg 2 hours following infection improved survival from 50% to 100%. The MOTS-c treated mice had reduced bacterial loads and a dampened proinflammatory cytokine response. Meanwhile, MOTS-c increased the bactericidal capacity of macrophages, and evidenced by increased expression of the pattern recognition receptor dectin-1. This suggests that MOTS-c may reduce the risk for infection-related mortality. Pre-treatment with exogenous MOTS-c (20 mg/kg 4 hours prior to LPS) also improved survival from 30% to 65% in a mouse model of LPS-induced sepsis [37]. This was accompanied by an attenuation of BBB permeability and neuroinflammation.

Senescence: UNCLEAR
In cultured human fibroblasts induced to become senescent, MOTS-c levels increased following the induction of senescence [38]. Treatment with MOTS-c enhanced beta oxidation of fatty acids and the mitochondrial respiration of the senescent cells, which contributes to their maintenance. MOTS-c also promoted expression of pro-inflammatory cytokines associated with the senescence associated secretory phenotype (SASP) in these culture senescent cells. However, a separate study found that MOTS-c levels declined in senescent pancreatic cells and that MOTS-c treatment (0.5 mg/kg/day, i.p.) protected against pancreatic β-cell senescence in mouse models of type 1 diabetes (NOD mice) and type 2 diabetes (induced by the insulin-receptor antagonist, S961) [39]. Treatment of isolated pancreatic islets with exogenous MOTS-c also lowered expression of senescence and SASP markers. This suggests that the impacts to senescence may be context dependent, based on cell type and/or experimental conditions.

Aside from the MOTS-c analog CB4211, CohBar developed several other mitochondrial derived peptide analog-based therapeutics. However, due to the dissolution of CohBar, the future development of these assets appears unlikely.

CB5064 analogs

Obesity: CB5064 analogs activate the apelin receptor (APJ/AGTRL1/APLNR) with an EC50 in the low micromolar range [40]. The endogenous ligand, apelin, is an adipokine. In a mouse model of diet-induced obesity, CB5064 analogs reduced body weight, with a selective reduction in fat mass, and improved glucose tolerance.

Acute respiratory distress syndrome: In an LPS mouse model of acute respiratory distress syndrome, treatment with CB5064 analogs prior to LPS, reduced fluid accumulation in the lungs and levels of pro-inflammatory cytokines (IL-β, KC/GRO, IFN-γ, IL4, IL6, TNFα, IL2, IL9) in the lung fluid [41].

MBT5 Analogs

Cancer: MBT5 analogs are antagonists of the chemokine receptor CXCR4, which is involved in hemopoietic stem cell homing and cell proliferation [42]. Inhibition of CXCR4 can enhance the efficacy of chemotherapy by mobilizing immune cells. The company had reported that the addition of subcutaneously administered MBT5 analogs led to a greater reduction in tumor growth relative to the chemotherapeutic temozolomide in a B16F10 syngeneic tumor mouse model of melanoma.

MBT2 (CB5138-1)

Idiopathic Pulmonary Fibrosis: In a bleomycin-induced mouse model of idiopathic pulmonary fibrosis, treatment with CB5138 reduced lung fibrosis, lymphocyte infiltration, and collagen content. CB5138 also reduced the expression of fibrosis markers in primary human lung fibroblasts [43].

Safety: MOTS-c therapeutic safety has not been established. The analog CB4211 was safe in a short-term study, but persistent injection site reactions were common. MOTS-c may interact with other drugs that target AMPK.

Types of evidence:

- 1 Phase 1a/1b clinical trial in healthy volunteers and subset with fatty liver disease for CB4211
- Numerous laboratory studies

MOTS-c has not been clinically tested in humans as a therapeutic peptide, and preclinical models have not thoroughly evaluated its safety. Endogenous MOTS-c is associated with favorable metabolic

adaptations. Exogenous MOTS-c recapitulates many of these metabolic adaptations in preclinical models, with effects appearing to be proportional to the degree of metabolic dysfunction, such that young healthy animals show only marginal improvements, while aged and overweight animals show evidence of metabolic rejuvenation [4]. It has not been established whether there is a level of MOTS-c or conditions under which MOTS-c can become maladaptive.

MOTS-c primarily acts as an activation or AMPK; thus, its efficacy profile overlaps with the drug metformin, which also activates AMPK [2]. It is not clear whether the prospective side effect profile would also be similar since metformin can also act on other pathways. Additionally, the primary site of action for MOTS-c is the skeletal muscle, while the liver is the primary site of action for metformin.

Sex effect: MOTS-c shows a sex effect in that its levels are more heavily impacted by metabolic dysfunction in males than in pre-menopausal females, which likely stems from the influence of ovarian hormones, such as estrogen [16; 23]. It is unclear whether MOTS-c based therapeutics would have equal efficacy in men and women, as the available evidence suggests that men may experience more benefit. Different dosing may also be required in men and women. Additional research is needed to address this issue.

The MOTS-c peptide analog CB4211 has been tested in a Phase 1a double blind, placebo-controlled single ascending dose and multiple ascending dose clinical trial in healthy adults (NCT03998514). It was found to be safe and well tolerated after 7 days of dosing (Press release). The trial had been temporarily suspended in 2018 to address persistent mild injection site reactions (persistent painless bumps), which may be related to evidence that some of the CB4211 remains at the injection site (Press release). Following an amended protocol, the Phase 1a study resumed and was completed in 2019. The Phase 1b study in subjects with obesity and fatty liver disease was temporarily paused in early 2020 due to the covid pandemic (Press release), but resumed later that year and was completed in 2021. Full safety data have not been disclosed, but topline results reported by CohBar indicate that CB4211 met its primary endpoint of safety, and was well-tolerated with no serious adverse events (Press release).
In healthy young male and female mice, 7 days of CB4211 at doses ranging from 15 to 250 mg/kg/day (i.p.) did not have any effects on weight [26].

According to the U.S. Anti-Doping Agency (USADA), the long-term safety of MOTS-c is unknown, but reported side effects of self-experimenters include increased heart rate or heart palpitations, injection site irritation, insomnia, and fever. MOTS-c is banned for use in sport by the World Anti-Doping Agency.

Drug interactions: Since the primary mechanism of action involves the activation of AMPK, MOTS-c is expected to interact with other AMPK activating drugs, primarily antidiabetic drugs, such as metformin.

Sources and dosing:

MOTS-c has not been approved for use in humans and is available as a research grade product from commercial suppliers. In preclinical studies administration is primarily intraperitoneal, and self-experimentation reports have used subcutaneous or intramuscular administration. Therapeutic dosing for MOTS-c has not been established; higher levels of endogenous MOTS-c are associated with better metabolic health parameters, but it is unclear if there is an upper limit. The normal range of MOTS-c levels in a healthy population has not been established, as there is a wide variation in the reported levels of plasma MOTS-c across studies from around 150 pg/mL to around 580 ng/mL, though the latter was in children and adolescents, who would be expected to have higher levels [2; 4; 6; 16; 30]. In a reference population of 10 males and 10 females, plasma MOTS-c levels ranged from 45.9 to 218.5 ng/mL when measured by ELISA, but these values could not be confirmed when measured via LC/MS [6]. The variation may stem from technical issues. MOTS-c is typically measured via ELISA, which may not be optimal for reproducibility. MOTS-c is also extremely unstable, with levels decreasing by one-quarter when stored at 4°C for 24 hours and by 85-90% when stored at room temperature for 2 to 3 hours [6].

Stability analyses of exogenous MOTS-c peptides were conducted using high-resolution mass spectrometry by Mohtashami et al [44]. They assessed the oxidation of methionine of MOTS-c as a measure of degradation. According to their work, MOTS-c that had been reconstituted in water was stable, with no significant degradation for at least 30 days when stored at 4°C.

MOTS-c is expected to have a short half-life *in vivo*, though the biological half-life of exogenous MOTS-c peptides in humans have not yet been established. Endogenous MOTS-c is induced in response to exercise. Levels increase robustly within the muscle and appear to persist. The exercise-induced increase in circulating levels, on the other hand, returns to baseline within 4 hours, suggestive of a half-life of 1 to 2 hours, depending on individual metabolic rates [45]. Therefore, the duration of biological activity for exogenous MOTS-c likely depends on how much is taken up into cells/tissues, where it may persist long enough to meaningfully impact cell physiology, and how much remains in circulation to be cleared relatively rapidly. We currently do not have reliable information about how much of the exogenous MOTS-c is taken up into cells, if it is preferentially taken up by certain cell types, and how long it lasts, or

the durability of its effects. Without this information, it is difficult to determine a potentially effective dosing strategy.

As of September 2023, the FDA no longer allows the compounding of MOTS-c by compounding pharmacies for human use due to including in Section 503A Category 2 of bulk drug substances (FDA). Category 2 represents bulk drug substances that raise significant safety risks and thus 503A (i.e. compounding) pharmacies should avoid compounding substances on that list (FDA).
According to the FDA "Compounded drugs containing MOTs-C may pose significant risk for immunogenicity for certain routes of administration and may have complexities with regard to peptide-related impurities and API characterization. FDA has not identified, any human exposure data on drug products containing MOTs-C administered via any route of administration. FDA lacks important information regarding any safety issues raised by MOTs-C, including whether it would cause harm if administered to humans."

In the Phase 1b trial in patients with obesity and fatty liver disease, CB4211 was administered at a dose of 25 mg per day via subcutaneous injection for four weeks (Press release).

Research underway:

There are currently no clinical trials testing MOTS-c or MOTS-c analog peptides.

Search terms:
Pubmed, Google: MOTS-c

- Alzheimer's disease, cognition, aging, lifespan, cardiovascular, diabetes, metabolism, exercise

Websites visited for MOTS-c:

- Clinicaltrials.gov
- PubChem

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