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Review

CONCEPT OF METABOTROPHINS: BEGINNING AND PROSPECTIVE GROWTH

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Since 2003, we have been focusing on metabotrophic factors (MTF), collectively named metabotrophins (MTs) (from Greek metabole – "a change", and trophe – "nutrition", means "nutritious for metabolism"). These are signaling proteins which improve glucose, lipid and energy metabolism, also affect positively cardiovascular and cognitive functions. They derived from various tissues, we focused on those secreted by adipose and skeletal muscle tissue. Examples include NGF, BDNF, NT-3, FGF21, GDF11, adiponectin, leptin, irisin, visfatin, meteorin, sirtuin-2, Klotho, etc. The present review highlights the beginning and perspective growth of our concept of a pivotal role of MTs in the pathogenesis and therapy of obesity-related cardiometabolic diseases (e.g., atherosclerosis, hypertension, obesity, type 2 diabetes mellitus and metabolic syndrome) and neurometabolic diseases (e.g., Alzheimer's disease, Parkinson's disease, and multiple sclerosis). ***Biomed Rev*** **2022; 33: 67-75.**

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INTRODUCTION

The new paradigm is always better, *not just different*.
Thomas Kuhn, *The Structure of Scientific Revolutions, 1962*

Thomas S. Kuhn's 1962 book was a landmark event in history and philosophy of scientific knowledge (epistemology). Kuhn challenged the then prevailing view of "normal science" which was viewed as "development-by-accumulation" of accepted facts and concepts leading frequently to *epistemological paralysis*, we dubbed it *neophobia*. Kuhn argued for a model in which a period of such conceptual continuity in normal science were interrupted by a period of revolutionary science leading to a new paradigm, an event he designated *paradigm shift*.

The pathobiology and therapy of obesity-related cardiometabolic diseases (CMD) and neurometabolic diseases (NMD), particularly Alzheimer's disease (AD), are immensely complex at the genetic, cellular and molecular levels. This scenario raises the question of how such a multiplexity may be grappled in a more tangible manner.

Man gave names to all the molecules
In the beginning, in the beginning
Man gave names to all the molecules
In the beginning, long time ago…
Paraphrase from Bob Dylan's lyrics

In the beginning, 19 years ago, our article titled "Metabotrophic potential of neurotrophins: implication in obesity and related diseases?" was published (1). From this time onwards, we have been focusing on metabotrophic factors (MTF) and, in analogy with neurotrophins, gave them name *metabotrophins* (MTs) (from Greek *metabole* and *trophe*, means "nutritious for metabolism") (2-10). Metabotrophins are signaling proteins which improve glucose, lipid and energy metabolism, also cardiovascular and cognitive functions, thus exerting *metaboprotective actions*. Metabotrophins derived from various tissues, we have been focusing on those secreted (synthesized, processed, and released) by adipose and skeletal muscle cells. Selective examples of such adipokines, myokines and/or adipomyokines include NGF, BDNF, NT-3, FGF21, GDF11, adiponectin, leptin, irisin, visfatin, sirtuins, Klotho, meteorin, *etc*, most of them mediating both metabotrophic and neurotrophic effects.

Current epidemiological studies suggest that obesity and diabetes mellitus are associated with a >4-fold increase risk of developing AD. Obesity, a major risk factor for CMD, is most prevalent human health disorder globally. According WHO, in 2016 more than 1.9 billion adults aged 18 years and older were overweight (BMI 25.0–29.9 kg/m^2) worldwide. Of these over 650 million adults were obese (BMI over 30 kg/m^2). The worldwide prevalence of obesity nearly tripled between 1975 and 2016.

There is now solid evidence that type 2 diabetes mellitus (T2DM) is strongly associated with the obesity, hence the term "diabesity" has been introduced. In such a cascade of diseases, diabesity, metabolic syndrome and atherosclerosis could be associated with AD (T3DM).

Mainstream therapies, such as statins, metformin and antithrombotics, can improve some symptoms in CMD, but do not slow enough progressive atherosclerotic plaque vulnerability and other manifestations of CMD. Despite intensive research, potential interventions have not demonstrated consistent metaboprotective effects. Thus, patients with CMD, also with AD, develop severe metabolic degeneration with the resulting morbidity and mortality rates.

The present review highlights the beginning and perspective growth of our concept of a pivotal role of MTs in the pathogenesis and therapy of obesity-related CMD and NMD.

PARADIGM SHIFTS IN ADIPOBIOLOGY

Recently, one of the challenges in the study of CMD and NMD is their association with the "rediscovery" of a neglected tissue, the adipose tissue. Adipose tissue is recognized as a vital player not only in its "classical" control of lipid and energy metabolism, but also of inflammation, immunity, reproduction as well as cardiometabolic and neuronal biology. Adipose tissue is a cellular and extracellular matrix assembly composed of adipocytes, fibroblasts, immune cells and matrix components, also rich in sympathetic nerves, blood vessels, and stem cells.

There are three major subtypes of adipose tissue: white adipose tissue (WAT), brown adipose tissue (BAT) and brown-in-white (BRITE) adipose tissue (11-15). Severe metabolic consequences can result from excessive WAT gain, featuring obesity and related CMD, or extreme loss of WAT mass, known as lipodystrophy. WAT is a major metabolic and secretory tissue, whereas BAT is responsible for thermogenesis.

White adipose tissue is a *bona fide* endocrine and paracrine organ secreting more than 500 signaling proteins collectively termed adipokines (11, 12). Some of them are mediators of the cross-talk WAT-brain in regulating food intake and energy homoeostasis. However, the hypothalamus is not the only brain target for adipokines, and food intake is not the only biological effect of these signals. Rather, some adipokines take part in the

process of inflammation, immunity, and cognition.

At epistemological level, the adipose tissue has undergone several paradigm shifts in last 30 years. And take center stage in so many diseases that it leaves most scholars and medical doctors astonished.

The first paradigm shift is illustrated in Table 1.

Table 1. *A paradigm shift: never before has adipose tissue been so active.*

FROM
Adipose tissue is a lipid and energy storage involved in obesity
TO
Adipose tissue is an endocrine and paracrine organ
– Secretes metabotrophic factors, neuropeptides, neurohormones
– Secretes steroid hormones
Adipose tissue is an immune organ
Adipose tissue is a source of and target for inflammatory mediators
Adipose tissue produces all components of rennin-angiotensin system
Adipose tissue produces amyloid precursor protein, neprilysin and other AD-related proteins*
Adipose tissue is thus involved in numerous diseases beyond obesity

* This raises a question whether these AD-related proteins may spread to the brain and thus be involved in the pathobiology of AD.

The publication of a ground-breaking article describing the discovery of leptin, an adipose-secreted hormone, by Jeffrey Friedman and colleagues, marked such a revolutionary event, Fat's Big Bang, in the study of adipose tissue and obesity (*Nature* 1994; 372: 425-432. DOI:10.1038/372425a0). In this context, the pioneering contribution of Douglas Coleman (1931-2014) has to be acknowledged. His work established the first clues to a genetic component in obesity. In the 1970s, Coleman conducted a series of experiments that led him to propose the existence of a *satiety factor* that would account for obesity and T2DM among certain laboratory mice.

Onwards, the term *adipokines* instead of adipocytokines was introduced and in 2003 the research field studying adipose tissue in health and disease was conceptualized as *adipobiology and adipopharmacology* (11).

Another paradigm shift features the increasing significance of BAT in health and disease. In human body, WAT stores lipids and secretes numerous adipokines (and other bioactive molecules) (11, 12), whereas BAT produces heat and secretes few adipokines (13-15). BAT-mediated increase in energy expenditure is realized by uncoupling respiration from ATP synthesis *via* uncoupling protein 1 (UCP1) expressed in the inner mitochondrial membrane of brown adipocytes, thus mediating a process known as adaptive thermogenesis. Animal studies have shown that activation of BAT counteracts diet-induced weight gain and related disorders such as T2DM and metabolic syndrome; it may also be the case for humans. Hence, brown adipobiology is emerging as a new challenge for biomedical research.

In brief, BAT is the major thermogenic organ, whereas WAT is the body's largest lipid storage and the most productive – endo- and paracrine – organ delivering multiple adipokines, BDNF, FGF-21, adiponectin and irisin being secreted by both adipose and skeletal muscle tissue (6, 7, 14-18). Last but not least, a subset of white adipocytes can be activated to thermogenic brite adipocytes. This conversion is enhanced by the drug Mirabegron, a β3 adrenoceptor agonist, resulting in improved glucose, lipid and thermogenic homeostasis. "These exciting initial results could be a forerunner for additional studies on the pharmacotherapy for human obesity and related cardiometabolic disorders" – to cite Sridhar and Lakshmi (19). Hence, β3 adrenoceptor agonists might be considered as examples of pharmaceutical MTs.

Briefly, accumulated, inflamed, dysfunctional WAT is a pathogenic (metabodegenerative), whereas activated BAT is a sanogenic (metaboprotective) biological event. Moreover, activated skeletal muscles secrete myokines, some of them also produced by adipose cells named adipomyokines – most of them exert metabotrophic intelligence (4).

PARADIGM SHIFTS IN NEUROTROPHINS

At the end of the 19th century it was envisaged by Santiago Ramon y Cajal but has not been proved that the nerves require trophic support. By a rare combination of scientific reasoning and intuition, Rita Levi-Montalcini (1909-2012) obtained the proof in 1951 in Washington University in Saint Louis, MO, USA, where she have discovered the first cell growth factor, namely NGF. And in 1986, 35 years later, awarded Nobel Prize in Physiology or Medicine. Cumulative data of NGF have been embodied in the conceptual framework of the neurotrophic theory. It reveals a pivotal role of effector cells in the control of neuronal differentiation, survival and function *via* production of NGF.

The past four decades has witnessed a number of paradigm shifts in the study on NGF and the related neurotrophins BDNF, neurotrophin-3 (NT-3), NT 4/5, and NT-6. Studies have re-

A photograph showing Luigi Aloe, RLM and George N. Chaldakov (GNC) taken after GNC's lecture presented at the Symposium dedicated to 100-th birthday of RLM held on 21 April 2009 in Rome. It was an enjoyable intellectual event of ciencia e amicizia.

vealed that these neurotrophins, particularly NGF, BDNF and NT-3, not only stimulate nerve growth and survival, but also exert extraneuronal trophic effects on (i) immune cells, (ii) keratinocytes, enterocytes and prostate and breast epithelial cells, (iii) endothelial cells, acting as angiogenic factors, and (iv) lipid, glucose and energy metabolism, acting as MTs (1-10).

As often occurs, the framework of an initial concept of the physiological role of a newly discovered molecules extends in the light of emerging findings. This was also the case with the neurotrophins (and adipokines). As mentioned above, the functional signature of NGF, BDNF and NT-3 was enriched with one more expression – metabotrophic actions on glucose, lipid, energy and pancreatic beta cell, also cardiovascular and neuronal homeostasis. The proof-of-concept was based on results demonstrating that the circulating and/or tissue levels of NGF and BDNF are commonly decreased in atherosclerosis and metabolic syndrome (16), acute coronary syndrome (20, 21), depression and other neuropsychiatric diseases (5, 18), including AD which increasingly is considered T3DM (7, 22, 23). A selected list of MTs (Table 2) and metabotrophic action of NGF and BDNF (Table 3).

Table 2. *A list of endogenous metabotrophins and their roles in type 2 diabetes mellitus (T2DM), obesity, CMD, and inflammation. From: (7).*

	Expression Levels			Role in		
	Obesity	Exercise	T2DM	Obesity	CMD	Inflammation
Adipsin	↑↓	≈ or ↓	↓		↑	
Leptin	↑	↓	↓	↓	↓	↑
Adiponectin	↓	↑	↓	↓	↓	↓
NGF/BDNF	↓	↑	↓	↓	↓	
Irisin	↑	↑	↓	↓	↓	↓
Klotho	↓	↑	↓	↓		↓
FGF21	↑	↑	↓	↓		
GDF11	≈ or ↑↓	≈ or ↑	↓	↓	↓	↓
Meteorin-like (Metrnl)	↓	↑	↓	↓		↓
FSTL-1	↑	↑	↑		↓	↑
Visfatin	↑	↑	↓	↑↓		↑
Humanin	↓	↑	↓		↓	
Omentin	↓	↑	↓	↓	↓	↓
Angiopoietin-like protein 4	↑	↑	↓		↑	
Aquaporin-7 *	↑	↑	↓	↓	↓	
Incretins (GLP-1 and GIP)	≈ or↓	↑	↓	↓	↓	
Kisspeptin-1	↓	↓	↓		↑	
Progranulin	↑	≈	↑	↑	↓	↑
Kallistatin	↓				↓	↓
Neprilysin	↑		↓		↓	↓
Myonectin	↓	↑	↓		↓	↓

Symbols: ≈ unchanged, ↓ decrease/amelioration, ↑ increase/exacerbation, ↑↓ inconclusive.

*Some drugs such as Mirabegron, a β3 adrenoceptor agonist (19), and metformin (24) may be considered pharmaceutical MTs. And caloric restriction, also polyphenols (25) – nutraceutical (bioceutica) MTs.

Table 3. *Metabotrophic NGF and BDNF. From: (7).*

NGF shares homology with proinsulin
NGF and BDNF are produced by pancreatic beta cells and exert insulinotropic effect
NGF and BDNF are trophic factors for pancreatic beta cells, also improve beta cell transplantation
NGF up-regulates expression of LDL receptor-related protein
NGF up-regulates expression of PPARγ
NGF inhibits glucose-induced down-regulation of caveolin-1
NGF improves skin and corneal wound healing*
NGF rescues silent myocardial ischemia in diabetes mellitus
NGF improves diabetic erectile dysfunction
NGF and BDNF suppress food intake
Healthy lifestyle increases brain and/or circulating levels of NGF/BDNF
Atherogenic diet decreases brain BDNF levels
BDNF-deficient mice develop abnormalities similar to the metabolic syndrome
NGF and BDNF improves cognitive processes

*Note, if we consider the vulnerable atherosclerotic plaque as "vascular wound", then $TrkA^{NGF}$ agonists may stabilize the plaque preventing its rupture as discussed in one of the Perspectives in this volume of *Biomedical Reviews.*

METABOADIPOCRINOLOGY

Life of multicellular organisms requires interactions between cells of different tissues. Understanding how such interactions are associated with the lipid, glucose and energy metabolism account for cardio- and neurometabolic biology. The brain is a highly metabolic organ that is vulnerable to alterations in peripheral metabolism. This is extremely evident in obesity-associated adipose tissue dysfunction linked to adipokines which could accelerate brain aging and thus increase the risk of NMD, particularly AD (26). *In sensu stricto*, adipokines mediate the cross-talk between adipose tissue and hypothalamus in regulating food intake and energy homoeostasis. However, the hypothalamus is not the only brain target for leptin and food intake is not the only biological effect of this adipokine. By sending and receiving different types of protein and non-protein signals, adipose tissue communicates with many organs in the body (Fig. 1), thus contributing to the control of energy, lipid and glucose homeostasis as well as inflammation, immunity, learning and memory among many other biological functions.

In an attempt to "close" the metabotrophic loop in CMD and NMD, we found altered levels of NGF in pancreas and brain in streptozotocin-induced diabetes (27, also see 28). In the same stream, it was demonstrated that in response to experimental stress or diabetes, the amount of NGF and BDNF was altered both in WAT and BAT (15; Figs. 2, 3).

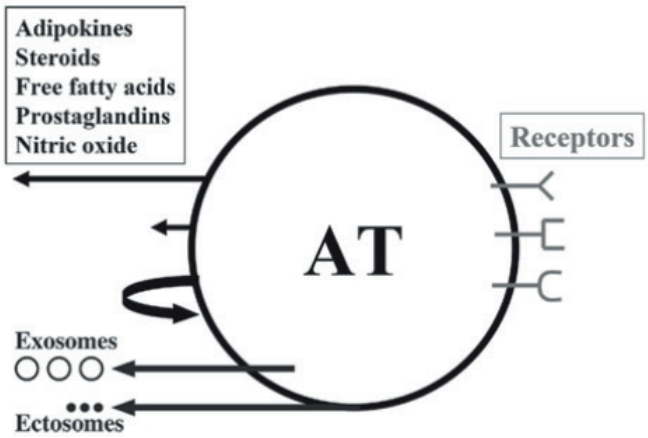

Figure 1. *Schematic illustration of white adipose tissue (AT) as a multicrine organ. AT consists of adipocytes, fibroblasts, mast cells, macrophages and other immune cells.The arrows, left from up-to-down, indicate endocrine, paracrine and autocrine pathways; the other two arrows show the extracellular vesicles: exosomes and ectosomes. Depicted on the right are the adipose cell receptors for various ligands. From: (7).*

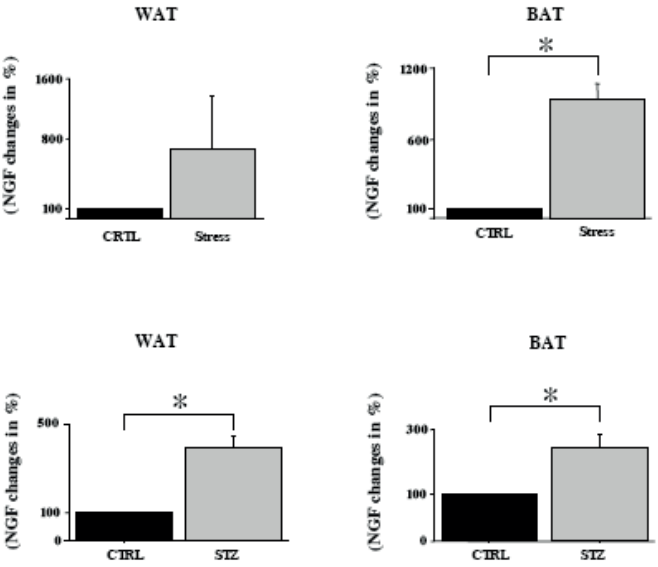

Figure 2. *Changes in the amount of nerve growth factor (NGF) in white adipose tissue (WAT) and brown adipose tissue (BAT) of controls compared to the concentration of NGF in stressed mice (Stress) and streptozotocin-induced diabetic rats (STZ), expressed as percentage of controls. Note the enhanced presence of NGF in WAT and BAT in stressed mice as well as diabetic rats. The vertical lines in the figure indicate pooled S.E.M. derived from appropriate error mean square in the ANOVA. * significant differences between groups ($p < 0.05$).* ***From:*** *(15).*

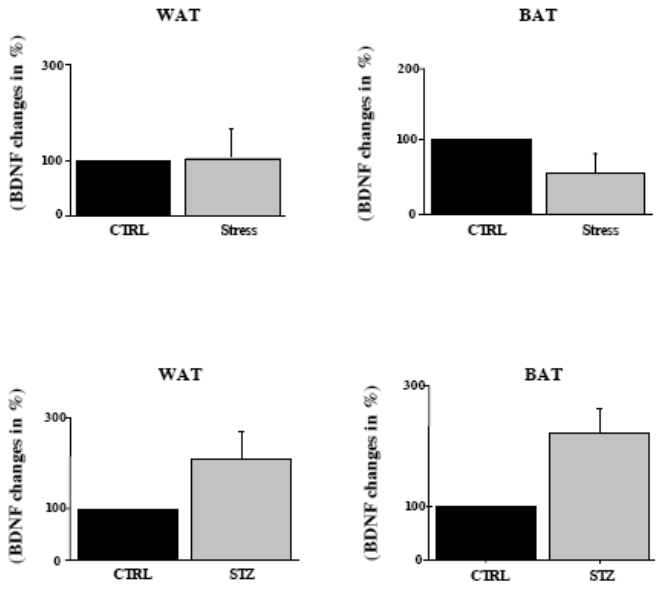

Figure 3. *Changes in the amount of brain-derived neurotrophic factor (BDNF) in epicardial white adipose tissue (WAT) and brown adipose tissue (BAT) of controls compared to the concentration of BDNF in stressed mice (Stress) and streptozotocin-induced diabetic rats (STZ), expressed as percentage of controls. The vertical lines in the figure indicate pooled S.E.M. derived from appropriate error mean square in the ANOVA.* ***From:*** *(15).*

PERSPECTIVES

The present concept is supported by data derived from other laboratories: (i) pancreatic beta cells secrete NGF and express its high-affinity receptor TrkA, findings being implicated in the pathogenesis of diabetes mellitus (29), and (ii) topical application of NGF accelerates healing of human skin and corneal ulcers, glaucoma, retinopathies and brain diseases (30). Further studies may open new windows for the search of *exogenous* MTs, such as (i) small molecules boosting secretory and/or signaling pathways of MTs, (ii) Mirabegron, a β3 adrenoceptor agonist (19), and (iii) incretin mimetics and receptor agonists, because the insulinotropic hormone glucagon-like peptide-1 (GLP-1) and exendin-4, a GLP-1 receptor agonist, exert neurometabotrophic effect (31, 32).

In support of these perspectives might be the recent discovery of (i) humanin, a mitochondria-derived peptide (33, 34), (ii) irisin, both myokine and adipokine, involved in the browning of WAT (35), (iii) SIRT2 (silent information regulator 2 protein, called sirtuin-2), NAD-dependent protein deacetylases related to visfatin (36), (iv) changes of the insulin signaling pathway including the down-regulation of insulin receptor substrate 4 (Irs4) as an early event in Alzheimer's disease (AD) (37-43, also see 44-46), (v) NGF role in processing of AAP (47, also see 48-50), (vi) exosomes and ectosomes, cell-derived extracellular signaling vesicles – the measurement of their presence in blood circulation as well as other body's fluid compartments has recently entered clinical and pharmacological laboratories for theragnostics purposes (51), (vii) NGF, BDNF and glial cells-derived neurotrophic factor in the pathogenesis and therapy of Parkinson's disease (52), (vi) NGF role in multiple sclerosis (53). The involvement of adipose tissue in the production, processing and exocytosis of AD-related molecules raises a question whether these proteins may spread *via* the blood circulation to the brain and thus be involved in the development of AD. Note, for Parkinson's disease it has been suggested that the alpha-synuclein misfolding might begin in the gut and spread *via* the vagus to the brain (54).

CONCLUSION

The present review suggests that understanding precisely molecular mechanisms of MTs may provide novel pharmaceutical and nutraceutical approaches for the therapy of CMD and NMD. For digital pharmaceuticals (digiceuticals) (55). Further studies may lead to or exclude the possibility that adipose tissue also „suffers" from AD, or at least extend our knowledge of viewing not only CMD but also AD as MT-deficit disorder (2, 7-9). Hence, the big question is: how can MTs be targeted for the purpose of the therapy of CMD and NMD? Possible answers at present might be via: (i) MT's receptor agonists (see about Trk-targeting agents in this volume of *Biomedical Reviews*), and (ii) boosting intracellular secretory pathways, thus increasing the circulating and/or local levels of MTs – both of these may represent a novel pharmacotherapeutic approach for CMD and NMD. At present, however, the knowledge of Palade-Blobel's secretory pathways (see Homage to George Palade in this volume of *Biomedical Reviews*) is not fully explored in MTs.

We hope the present concept might be *a better, not just different*. Future studies on MT's signature in CMD and NMD may therefore cultivate a more relevant thinking about how we can make MTs work for the improvement of metabolic and mental quality of life of *Homo sapiens* (Fig. 4).

Yet, we are keeping in mind Robert Frost's poem *The Secret Sits*:

We dance round in a ring and suppose,
But the Secret sits in the middle and knows.

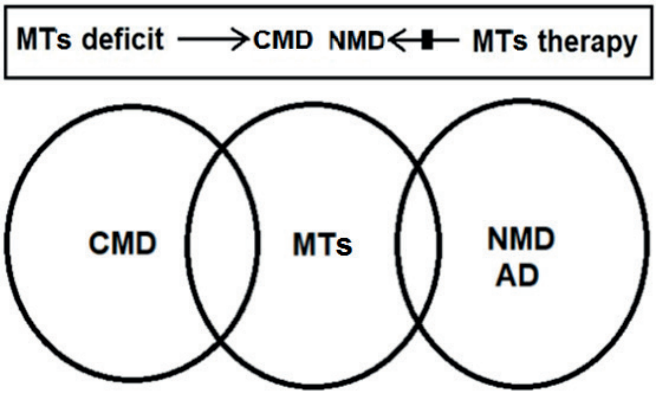

Figure 4. *Metabotrophins (MTs) on the cross-road of cardiometabolic diseases (CMD) and neurometabolic diseases (NMD), particularly Alzheimer's disease (AD). Credit for Nikifor N. Chaldakov. Modified from: (7).*

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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