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PROTOCOL

Challenges and Strategies in Metabolic Modulation Diets for Longevity: Protocol for the Validation of the FusionMed Antiaging Model

Retos y estrategias en dietas de modulación metabólica para la longevidad: Protocolo para la validación del modelo FusionMed Antiaging

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KEYWORDS

Metabolic regulation

Mediterranean diet

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ABSTRACT

Introduction: To develop and propose the validation of the FusionMed Antiaging (FMA) model, which combines principles from the Mediterranean (MD) and DASH diets with moderate caloric restriction and cultural adaptations to improve adherence and promote longevity and metabolic health.

Methods: A 12-week randomized controlled clinical trial is proposed with three groups: Standard Mediterranean Diet, Standard DASH Diet, and the experimental FMA model. Metabolic markers, adherence measures, and general well-being variables will be assessed using descriptive and inferential analyses. The intervention focuses on combining evidence-based principles, such as moderate caloric restriction and a personalized approach, to overcome cultural, economic, and behavioral adherence barriers, facilitating implementation in various settings. A total of 120 adults aged 40 to 70 years, with mild overweight (BMI between 25–30) and no severe metabolic diseases, randomly divided into three intervention groups

Results: The FusionMed Antiaging group is expected to show significant improvements in insulin sensitivity, systemic inflammation, body composition, and adherence compared to the control groups.

Conclusions: The FMA model presents itself as a promising and adaptable proposal to improve metabolic health and promote healthy aging. Its experimental validation will determine its efficacy and sustainability across diverse contexts and populations.

PALABRAS CLAVE

Regulación metabólica

Dieta Mediterránea

Dieta DASH

Longevidad

FusionMed Antiaging model

RESUMEN

Introducción: El objetivo es desarrollar y proponer la validación del modelo FusionMed Antiaging (FMA), que combina principios de las dietas Mediterránea (MD) y DASH con restricción calórica moderada y adaptaciones culturales para mejorar la adherencia y promover la longevidad y la salud metabólica.

Metodología: Se propone un ensayo clínico controlado aleatorizado de 12 semanas con tres grupos: Dieta Mediterránea estándar, Dieta DASH estándar y el modelo experimental FusionMed Antiaging. Se evaluarán marcadores metabólicos, medidas de adherencia y variables de bienestar general mediante análisis descriptivos e inferenciales. La intervención combina principios basados en evidencia, como la restricción calórica moderada y un enfoque personalizado, para superar barreras culturales, económicas y conductuales, facilitando su implementación en diversos entornos. La población objetivo serían 120 adultos entre 40 y 70 años, con sobrepeso leve (IMC entre 25–30) y sin enfermedades metabólicas graves, distribuidos aleatoriamente en tres grupos de intervención.

Resultados: Se espera que el grupo FusionMed Antiaging muestre mejoras significativas en la sensibilidad a la insulina, la inflamación sistémica, la composición corporal y la adherencia en comparación con los grupos de control.

Conclusiones: El modelo FusionMed Antiaging se presenta como una propuesta prometedora y adaptable para mejorar la salud metabólica y promover el envejecimiento saludable. Su validación experimental determinará su eficacia y sostenibilidad en diversos contextos y poblaciones.

KEY MESSAGES

1. The FusionMed Antiaging (FMA) model integrates metabolic modulation principles, moderate caloric restriction, and personalized strategies to improve adherence, making it a promising alternative for promoting longevity and metabolic health across diverse populations.

2. The proposed randomized clinical trial will evaluate FMA's efficacy and applicability, aiming to inform policies that reduce the burden of aging-related chronic diseases through scientifically validated dietary interventions through increased dietary adherence, cultural adaptation and sustainability that could improve metabolic markers

CITATION

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INTRODUCTION

Caloric restriction (CR) involves reducing caloric intake without causing malnutrition. It is a widely studied strategy due to its benefits for health and longevity[1]. In preclinical models, CR has been shown to extend lifespan and improve health by inducing metabolic and cellular adaptations that protect against chronic diseases associated with aging[1].

In humans, caloric restriction (CR) has been shown to modulate key metabolic pathways such as AMPK and mTORC1, mechanisms also associated with cellular regeneration and autophagy. Furthermore, dietary modulation of amino acid intake—particularly branched-chain amino acids and methionine—has been linked to reduced mTORC1 activation, supporting metabolic regulation and healthy aging outcomes[2].

In animals, CR activates pathways such as AMPK and mTORC1, promoting autophagy, a critical mechanism for cellular regeneration[3]. Additionally, the limitation of amino acids, such as branched-chain amino acids and methionine, reduces mTORC1 activity, enhancing cellular health and metabolism[2].

In humans, while direct evidence of CR's impact on longevity is limited, it has been shown to improve insulin sensitivity, regulate circulating lipids, and reduce inflammation, thereby decreasing the incidence of chronic diseases such as type 2 diabetes, cancer, and cardiovascular diseases[4, 5]. Studies like CALERIE have linked CR with improvements in metabolic markers, such as lower LDL cholesterol, reduced inflammation, and greater insulin sensitivity[5, 6].

CR has also been observed to reduce oxidative stress and improve sleep and mood in older adults, although it may cause adverse effects like decreased bone density, highlighting the importance of adequate monitoring[7].

Culturally, the Okinawan diet exemplifies the benefits of moderate energy restriction, with a caloric intake 15-20% lower than the Japanese average. This is associated with greater longevity and a lower incidence of degenerative diseases[1]. This example demonstrates how a balanced hypocaloric diet can enhance quality of life.

CR also increases the activity of sirtuins and promotes mechanisms such as autophagy and mitophagy, protecting against oxidative damage and the accumulation of senescent cells[3]. This contributes to reducing chronic inflammation and improving immune and metabolic function.

In conclusion, CR is an effective intervention for promoting health during aging, but its application faces challenges such as individual variability and low long-term adherence. It is essential to explore sustainable dietary patterns, such as the Mediterranean Diet (MD) and DASH, which combine the benefits of CR with a more accessible approach[4, 5].

In this context, this study introduces the FusionMed Antiaging (FMA) model, which integrates principles of the MD and DASH with metabolic modulation strategies. The main objective is to develop and validate an innovative dietary model that promotes longevity through a sustainable and customizable approach. Through a randomized clinical trial, the effects of FMA on metabolic markers, adherence, and overall well-being will be evaluated, positioning it as a promising alternative for healthy aging.

Challenges in the Implementation of Energy-Restrictive Dietary Patterns

Energy-restrictive diets and fasting patterns, while beneficial for longevity and health, face significant adherence challenges due to social, cultural, and behavioral factors. Food fulfils nutritional needs but is also a source of pleasure, tradition, and socialization, which can conflict with the perceived "deprivation" associated with caloric restriction, especially in contexts where food abundance is deeply rooted in cultural activities[1,3] impacting long-term sustainability. These barriers are less evident in animal models, where interventions are applied under controlled conditions, free from cultural or social influences, allowing for the observation of benefits such as metabolic improvements and increased longevity[2].

In humans, genetic variability, diverse lifestyles, and food traditions complicate the standardization and adaptation of caloric restriction (CR) and fasting to individual contexts. Moreover, metabolic factors, such as reduced leptin and increased ghrelin levels, intensify hunger, further complicating adherence[6].

The pleasure derived from foods rich in fats and refined carbohydrates, which activate brain reward centers, makes the transition to hypocaloric diets more challenging. Changes in dietary habits also disrupt eating rhythms, causing discomfort and leading to abandonment of these regimens[7].

Finally, dietary habits shaped by culture, tradition, and environment hinder the adoption of restrictive patterns. Changing established routines requires significant behavioral restructuring, generating resistance in societies with food abundance[8].

In summary, cultural, social, economic, and metabolic factors affect adherence to restrictive patterns. This highlights the need for sustainable metabolic modulation approaches tailored to individual lifestyles to foster prolonged and effective adherence[5, 7, 8].

Metabolic Regulation and Anti-Aging Dietary Design

Metabolic modulation involves adjusting nutrients to activate or inhibit key molecular pathways that promote longevity and health during aging while avoiding malnutrition. By manipulating macronutrient intake and energy-restrictive patterns, this strategy aims to replicate the benefits observed in animal models and apply them practically to humans. Its objectives include reducing oxidative stress, improving mitochondrial health, and decreasing cellular senescence without requiring pharmacological interventions[1, 2].

This nutritional approach affects metabolic pathways such as AMPK and mTOR, promoting adaptive cellular responses. AMPK, activated by low energy availability, regulates glucose and lipids, inhibits mTORC1, and fosters autophagy, which is essential for cellular renewal[2,3]. In contrast, excessive activation of mTOR accelerates cellular damage, while its inhibition through amino acid and carbohydrate restriction promotes autophagy, reduces inflammation, and mitigates oxidative stress[3].

Patterns like the Mediterranean Diet (MD) and DASH have shown significant benefits. The MD, rich in fruits, vegetables, legumes, fish, and healthy fats, reduces animal proteins in favour of plant-based proteins, limiting branched-chain amino acids and inhibiting mTOR[1,4]. The DASH diet, designed to reduce hypertension, emphasizes plant-based foods, whole grains, and low-fat dairy products, improving insulin sensitivity and regulating mTOR[1, 5].

Studies like PREDIMED have highlighted that the MD reduces cardiovascular and neurodegenerative risks due to its antioxidant and bioactive compound content[5,6,9]. Similarly, DASH improves blood pressure, lipid profiles, and insulin sensitivity, reducing the risk of metabolic and neurodegenerative diseases[5,6,7,10].

Another notable example is the Okinawan Diet, characterized by a caloric intake 15–20% lower than the Japanese average, with foods rich in antioxidants and nutrients, which is associated with greater longevity and a lower incidence of chronic diseases[11,12]. Additionally, Blue Zone diets share principles such as moderate caloric restriction and anti-inflammatory profiles, which are strongly linked to longevity[13,14,15,16].

In summary, metabolic modulation through patterns like MD, DASH, and the Okinawan Diet improves metabolic markers and activates anti-aging mechanisms like autophagy. However, their effectiveness depends on sustainability and adaptability to real-world contexts, underscoring the need for personalized dietary designs to maximize adherence and anti-aging benefits.

Development of the FusionMed Antiaging (FMA) Model

The personalization of dietary design is crucial to optimizing adherence to anti-aging interventions. Adapting diets to metabolic needs, cultural preferences, and individual lifestyles enhances both their feasibility and effectiveness, maximizing long-term benefits.

Strategies such as caloric restriction (CR) and intermittent fasting (IF) are effective in preventing chronic diseases and delaying aging but face barriers related to cultural restrictions, food enjoyment, and inherited eating behaviors[1]. Designing interventions tailored to individual preferences and cultural contexts increases their likelihood of success, while nutritional education and continuous support improve understanding of their benefits and foster motivation to maintain them.

IF and time-restricted feeding (TRF) are complementary strategies to CR. TRF limits food intake to 8–10 hours daily, promoting prolonged fasting periods that regulate glucose, reduce insulin levels, and improve cardiovascular biomarkers by aligning meals with circadian rhythms to enhance cellular regeneration[16,17,18]. Meanwhile, IF alternates normal days with restricted periods, activating metabolic pathways such as autophagy and mTOR regulation, which improve insulin sensitivity and reduce inflammation[8,19]. Although these approaches are flexible and promising, long-term adherence remains challenging.

Combining these strategies with established patterns like the Mediterranean Diet (MD) and DASH offers a sustainable and personalized approach. The FusionMed Antiaging (FMA) model integrates these strategies, also drawing inspiration from Blue Zone diets and principles of moderate caloric restriction to optimize longevity and health.

FMA prioritizes plant-based foods (80–90% of total intake), including fruits, vegetables, legumes, whole grains, and nuts, rich in bioactive compounds like polyphenols, which optimize metabolic health. It also incorporates wild plants (nettle, purslane, samphire) that add nutritional and culinary value. Protein intake is slightly reduced, favouring plant-based sources such as legumes, nuts, and seeds, while maintaining fish for its omega-3 content and limiting red meat to 5–6 servings per month[4,5]. High-glycemic-index carbohydrates are reduced, added sugars are eliminated, and healthy fats like extra virgin olive oil are prioritized.

This formula proposes moderate energy restriction tailored to individual needs, ensuring adequate intake of nutrients, antioxidants, and fiber essential for combating oxidative damage and inflammation. For example, older adults maintain higher protein intake to prevent sarcopenia, while younger populations emphasize caloric flexibility to avoid negative effects on basal metabolism.

FMA also prioritizes environmental sustainability. The use of artisanal fishing and reduced consumption of processed meats minimizes ecological impact, positioning it as an adaptable and scalable model that addresses both individual needs and global challenges.

Although based on theoretical principles and evidence from established patterns like MD and DASH[20,21], the application of FMA requires empirical validation. Experimental studies are needed to evaluate its metabolic effects, impact on longevity, and acceptance. In this context, an experimental design is proposed to validate the model's efficacy in a controlled setting, providing initial data for its future implementation.

METHODOLOGY

Validation of the FusionMed Antiaging Proposal

The aim of this clinical trial is to evaluate the metabolic efficacy, adherence, and practical viability of the FMA model. This analysis seeks to determine whether the model provides superior benefits in regulating key metabolic markers, improving body composition, and enhancing general well-being, while ensuring high acceptance and long-term adherence in a diverse population.

To achieve this, a randomized controlled trial[22] is proposed to compare the impact of the FMA model with two standard diets: the Mediterranean Diet and the DASH diet. Participants will be randomly assigned to one of three intervention groups, ensuring the validity of the results.

This design allows for a direct comparison of FMA's efficacy against established dietary patterns, minimizing biases and maximizing internal validity. The selection of participants with homogeneous characteristics (age, BMI, and metabolic health) ensures that the results are attributable to dietary interventions rather than external factors.

The study will provide preliminary evidence on the model's applicability within a representative population, laying the groundwork for larger and longer-term studies.

A population sample will be selected and divided equally into three groups. Recruitment will be conducted through primary care centers and public calls, ensuring representativeness of the target group. population according to defined criteria (see Table 1).

Study Design

A 12-week randomized controlled clinical trial is proposed to compare the effects of the FusionMed Antiaging (FMA) model against two standard dietary patterns: the Mediterranean Diet (MD) and the DASH diet. The study includes an initial two-week baseline phase, a twelve-week intervention phase, and a final reassessment phase. The objective is to evaluate the metabolic efficacy, adherence, and practical feasibility of the FMA model in a population of adults with mild overweight.

Target Population

The study will include 120 adults (40 per group), aged between 40 and 70 years, recruited through primary care centers and open calls. Participants must have a body mass index (BMI) between 25 and 30, and no severe metabolic diseases. Random allocation will ensure group comparability and minimize bias.

Inclusion and Exclusion Criteria

The criteria are presented in Table 1 and ensure a homogeneous sample in terms of baseline metabolic health. Individuals with advanced chronic diseases, severe food allergies, or pharmacological treatments that interfere with metabolism (e.g., corticosteroids, antipsychotics) will be excluded.

Interventions

Group 1 (Control - Standard Mediterranean Diet):

- Validated diet rich in fruits, vegetables, legumes, whole grains, and nuts.
- Extra virgin olive oil (EVOO) as the primary fat source.
- Moderate consumption of fish, poultry, and dairy products.
- Limited intake of red meat, processed foods, and added sugars.
- Moderate consumption of red wine or beer.

Group 2 (Control - Standard DASH Diet):

- Validated diet emphasizing fruits, vegetables, whole grains, and low-fat dairy products.
- Includes lean meats, fish, and legumes.
- Sodium limited to <2300 mg/day, with restrictions on saturated fats, added sugars, and processed foods.

Group 3 (Experimental - FMA):

- Moderate caloric restriction (15–20% below maintenance caloric needs), tailored to individual requirements.
- Low-glycemic-index carbohydrates and plant-based proteins (legumes, nuts, seeds), with reduced reliance on animal proteins.
- Controlled inclusion of small fish rich in omega-3 and low-fat dairy products.
- Use of healthy fats (EVOO).
- Reduction of processed and refined foods and inclusion of bioactive-rich foods.

Each group will receive a personalized weekly menu and participate in biweekly educational sessions to ensure understanding and adherence to the assigned dietary pattern. Evaluation variables are detailed in Table 2.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Adults aged 40 to 70 years	Pregnancy or breastfeeding
Body Mass Index (BMI) between 25 and 30 (mild overweight)	Diagnosis of advanced chronic diseases (renal or hepatic insufficiency)
Absence of uncontrolled severe metabolic diseases	Pharmacological treatments that may alter metabolism or body weight (steroids, antipsychotics)
Ability to attend regular follow-up sessions during the study	Severe food allergies or dietary restrictions incompatible with the studied diets
Willingness to follow the assigned dietary plan	Participation in another clinical trial within the past six months

Table 2. Variables measured and evaluation guidelines.

Category	Variables	Details
Metabolic Markers	Insulin Sensitivity (HOMA-IR) [26] Lipid Profile: Total cholesterol, LDL, HDL, triglycerides [27] Systemic Inflammation: CRP, IL-6 [28] Oxidative Stress: MDA, GSH	HOMA-IR assesses insulin resistance and type 2 diabetes risk. Lipid profile is associated with cardiovascular diseases. CRP and IL-6 are key indicators of systemic inflammation. MDA and GSH are markers of oxidative stress and cellular antioxidant capacity.
Adherence Measures	Food Frequency Questionnaires (FFQ) Weekly Dietary Records Satisfaction Scale Body Composition: Weight, BMI, fat/muscle mass	FFQ estimates adherence to dietary patterns. Weekly records monitor compliance. Likert scale measures diet acceptance. Bioimpedance assesses body composition.
General Well-Being	Sleep Quality (Pittsburgh Index) Mood (SF-36, emotional well-being) Perceived Energy (VAS scales)	Pittsburgh Index evaluates sleep quality. SF-36 measures emotional well-being. VAS quantifies perceived energy levels.
Sociodemographic	Age Sex Socioeconomic Level Educational Level	For subgroup analysis.

Procedure

Initial phase (2 weeks):

- Baseline evaluation of metabolic variables, adherence, and body composition.
- Random assignment to one of the three groups.

Intervention (12 weeks):

- Supervised diets with personalized weekly menus.
- Biweekly group sessions to promote adherence and address questions.
- Follow-up phase: Revaluation of all variables.

Final phase (2 weeks):

- Comprehensive reassessment of all measured variables and comparison of results among groups

During the intervention, specific strategies will be implemented to improve adherence:

- Nutritional education focused on the metabolic and longevity benefits of the model, including techniques such as motivational interviewing[23].
- Social and family support through peer networks and enabling environments.
- Cultural flexibility by incorporating local foods and traditional preparations.
- Promotion of sustainable behavioral change practices, such as mindful eating, short-term goal setting with incentives, and continuous professional monitoring of dietary records.
- Use of technological tools, including mobile applications for dietary tracking, online consultations with professionals, and gamification elements to foster motivation[24,25].

Variables and Measurements

The main variables include: (See Table 2)

- Metabolic markers: insulin sensitivity (HOMA-IR)[26], lipid profile (total cholesterol, LDL, HDL, triglycerides)[27], systemic inflammation (CRP, IL-6)[28], and oxidative stress and oxidative stress markers, including malondialdehyde (MDA) and reduced glutathione (GSH).
- Adherence: food frequency questionnaires (FFQ), weekly dietary records, satisfaction scale, and body composition (BMI, fat and lean mass via bioimpedance).
- General well-being measures: sleep quality (Pittsburgh Index), mood (SF-36, emotional dimension), and perceived energy (VAS scales).
- Sociodemographic variables: age, sex, educational level, and socioeconomic status.

Statistical Analysis

Descriptive statistics will be used to characterize the sample and compare baseline variables. Post-intervention comparisons between groups will be conducted using ANOVA or ANCOVA, adjusting for confounding variables. Regression models will identify predictors of adherence and outcomes. A qualitative analysis of satisfaction and perceived feasibility of the model will complement the results.

All analyses will be performed using a two-tailed significance level of $p < 0.05$, with both intention-to-treat and per-protocol approaches depending on adherence and dropout rates.

RESULTS AND DISCUSSION

Expected Results.

The experimental group (FMA) is expected to show significant improvements in metabolic markers and greater adherence compared to traditional diets, preliminarily validating the model as a viable alternative for promoting longevity and metabolic health. The experimental design will provide initial data on FMA's efficacy and adherence, supporting its practical viability and potential inclusion in healthy aging guidelines. Compared to MD and DASH, the model aims to optimize metabolic parameters and foster adherence through moderate caloric restriction and cultural personalization. The analysis will help identify necessary adaptations, such as adjustments in macronutrients, incorporation of traditional foods, and behavioral strategies, positioning FMA as a scalable solution for diverse populations.

Strategies to Improve Adherence

- Nutritional education[23]: Programs explaining the metabolic and longevity benefits of the model using tools aimed at dietary behavior change, such as motivational interviewing.
- Social support: Networks for sharing experiences and enhancing motivation.
- Family involvement: Creating an environment that supports adherence.
- Cultural flexibility: Incorporating local foods and adjusting to different contexts and sustainable Practices for Habit Changes
- Mindful eating: Teaching participants to recognize hunger and satiety signals.
- Rewards: Short-term goals with incentives to maintain motivation.
- Professional monitoring: Use of dietary records reviewed by professionals, use of Technology to Support Adherence[24]: Mobile applications for meal planning, food intake tracking, and immediate feedback; Online consultations in a continuous way and personalized support with specialists; and gamification[25] for incorporating challenges and motivational games.

Clinical Practice Implications

Cultural Contexts Adaptation: For mediterranean participants, adjust nutrients aligned with the MD model, prioritizing legumes and vegetables; for Asian participants, the incorporation of healthy fats and whole-grain versions of traditional cereals, and, for anglo-saxon cultures the gradual changes, such as reducing animal proteins.
Demographic Subgroups Adaptation: Older adults, menus with soft textures, rich in plant-based proteins and calcium. Low-income populations prioritize affordable and local foods; and for people with dietary restrictions offers alternatives to meet specific nutritional needs.
Practical Approach: Personalized menus and adaptation of recipes: adapted to each region or subgroup with the use of local ingredients. Along with educational workshops supported by culinary professionals to promote the pattern.
These strategies will facilitate acceptance in different contexts, providing a framework for future studies evaluating adherence and metabolic outcomes.
A key strength of this study is its innovative design: to our knowledge, it represents the first randomized controlled trial to directly compare the Mediterranean diet, the DASH diet, and the novel FusionMed Antiaging model in terms of both metabolic efficacy and dietary adherence. This comparative framework enhances the relevance, originality, and potential clinical impact of the findings in the field of nutritional strategies for healthy aging. The expected outcomes will contribute to refining the FusionMed Antiaging model and establishing a foundation for its integration into evidence-based dietary recommendations for aging populations

Study Limitations

While this study would provide valuable data, there are limitations:
- The duration (12 weeks) does not allow for evaluating long-term changes in chronic diseases or sustained adherence.
- The sample size (40 participants per group) limits generalization.
- Focus on adults aged 40–70 excludes other age groups.
- These limitations highlight the need for larger and longer studies.

Considerations for Future Studies

Macronutrient proportions should be individually adjusted. Reducing proteins in middle age to inhibit mTOR and increasing complex carbohydrates could favour longevity. Circadian modulation represents a promising field. Preliminary studies suggest that eating early optimizes metabolism and improves lipid profiles[29,30]. Additionally, modulation appears to influence longevity processes such as autophagy and DNA repair. Further studies are essential to confirm its impact on health and longevity[30].

CONCLUSION

Metabolic modulation based on MD and DASH, combined with moderate caloric restriction, is promising for promoting longevity. These diets activate key metabolic pathways, improving cellular health and preventing diseases.
The FMA model, based on sustainable and cultural principles, represents an accessible and personalized approach. Incorporating

techniques such as time-restricted feeding improves adherence without imposing extreme restrictions. However, long-term studies are needed to evaluate its impact on quality of life and longevity.

Ultimately, these strategies could form the foundation of sustainable dietary interventions, optimizing quality of life and longevity in diverse populations.

AUTHORS CONTRIBUTIONS

Study design, data collection: AM. Writing – original draft preparation: AM, BN and DL. Data analysis; AM, BN and DL. Writing – review and editing. All authors have read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest in the preparation of this manuscript.

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