nuttall women's health

Odessa

Ovarian Determinants of Sex-Specific Aging

Issued by: Nuttall Women's Health

Funding Scope and Duration

Odessa offers flexible support for projects ranging in duration from **one to three years**, with total funding requests **ranging from $500,000 up to $5,000,000 US dollars per project**. **NWH expects to fund several projects in the Odessa RFP.** Proposed budgets and timelines should be commensurate with the scope, ambition and stage of development of the project. Applicants are encouraged to carefully align their proposed work with the overall goals of the RFP and to demonstrate how the requested resources will enable meaningful scientific or technological advancement.

Goal

By building a rigorous, mechanistic understanding of ovarian aging, **Odessa** aims to uncover new pathways to preserve systemic health, enhance quality of life, and reduce the burden of chronic disease in women across midlife and into older age.

Desired Clinical Impact

A precision-based approach to optimizing health during midlife will become a reality. Molecular phenotyping will enable the identification of women in their 30s and 40s who are at risk for declining health—*women who would otherwise be overlooked by conventional definitions and diagnostic criteria for menopause*. Midlife symptoms and conditions will be redefined through a systems biology lens, focusing on how the aging ovarian secretome interacts with other physiological systems. This new understanding will pave the way for targeted interventions designed to alleviate the health burdens associated with the molecular event of ovarian aging and not limited by traditional clinical definitions of menopause. Therapeutic strategies—*no longer limited to conventional hormone replacement*—will be designed to enhance the protective effects of estrogen and other beneficial ovarian-derived factors, while also mitigating the harmful effects of dysfunctional or deleterious components of the ovarian secretome. These innovations will offer new pathways to improve long-term health outcomes for women as they age.

The Problem

While women live 5 to 6 years longer than men on average, they also spend a disproportionately greater share of those years—*up to 25% more*—in poor health or disability. This longevity advantage is accompanied by a paradox: women experience higher rates of chronic disease, functional decline and multisystem morbidity, particularly beginning in midlife. A striking inflection point in this trajectory occurs during the menopausal transition, when a cascade of biological changes dramatically accelerates age-related health risks.

Within five (5) to 10 years after menopause, the risk of coronary artery disease doubles, reflecting the abrupt loss of estrogen's protective cardiovascular effects and potentially other ovarian-derived factors. During this same period, women lose up to 20% of their bone mass, placing them at heightened risk for osteoporosis—a condition that is a major contributor to both frailty and mortality in older women. The postmenopausal window is also associated with a significant rise in the incidence of metabolic syndrome, insulin resistance and type 2 diabetes, as well as an elevated risk of neurodegenerative diseases such as Alzheimer's.

In addition to elevating long-term disease risk, the menopause transition is marked by a wide array of symptoms that significantly affect health and quality of life in the near term. These include vasomotor instability, sleep disruption, mood disorders, anxiety, cognitive challenges, musculoskeletal pain and

persistent fatigue. While these symptoms arise from profound biological changes, they may also act as early indicators or mediators of broader systemic dysfunction. However, a limited understanding of their biological basis has led to vague or dismissive labels—*such as "menopausal musculoskeletal syndrome" or "brain fog"*—that diminish the perceived seriousness of these conditions and hinder the development of precision-based interventions. Despite their prevalence and impact, these symptoms remain under-recognized, poorly characterized, and insufficiently treated.

Overwhelming evidence now positions menopause—*and the biological processes that underpin it*—as a critical driver of women's health decline in midlife and beyond. Yet, the biological architecture of menopause remains underexplored, particularly in relation to female-specific aging. The dominant medical and scientific frameworks have historically viewed menopause through the narrow lens of reproductive cessation, rather than as a complex, systemic aging transition that affects every major organ system.

State Of Current Knowledge

Historically, research on the ovary has been predominantly centered on its role in fertility, with the primary objective being the preservation of oocyte production. This narrow focus has effectively reduced the ovary to a binary organ—*one that either produces gametes or does not*. Unlike any other organ system, this binary framework oversimplifies ovarian physiology and fails to reflect the organ's dynamic and progressive biological trajectory across the lifespan.

In reality, ovarian function undergoes a continuum of changes beginning in pubescence, evolving through the reproductive years and extending into midlife and beyond. This aging process is not abrupt nor merely reproductive in consequence. Rather, it is part of a broader biological progression with significant implications for systemic health. Despite this biological truth, the prevailing paradigm has largely ignored the potential of the ovary to influence a wide range of physiological processes after its reproductive role ends. Given that most women will spend over half of their lives in a post-reproductive state with retained ovaries, this oversight represents a critical gap in our understanding of female health and aging.

The loss of reproductive capacity is traditionally linked with the menopause transition, defined clinically by the cessation of menses for a year. Biologically, the rise in follicle-stimulating hormone (FSH) is among the few recognized markers of this transition. Other markers, such as anti-Müllerian hormone (AMH), are often used to assess fertility potential rather than the broader context of ovarian aging. Furthermore, the assumption that non-follicle producing ovaries, *that remain in situ*, are no longer functioning organs in some biologically relevant manner has resulted in a stagnated understanding of female aging. This narrow clinical framework fails to capture the transitional and functional nuances of ovarian senescence. As a result, many women who experience symptoms and systemic changes indicative of ovarian aging (*which may represent that poorly defined time of perimenopause*) are not classified as menopausal, leading to a misalignment between clinical definitions, biological reality and individual symptomology.

To optimize women's health across the lifespan, it is essential to reframe ovarian aging as a central axis of female aging rather than a binary reproductive endpoint. Emerging research supports the integration of ovarian function into broader frameworks of systemic aging. While translational studies are exploring ways to stimulate follicular development to prolong fertility, these efforts, though informative, do not address the full scope of ovarian activity or its contributions beyond reproduction. Estrogen decline has been the dominant explanatory framework for suboptimal health for women in mid-life and undoubtedly estrogen is a critical mediator of long-term female health. Yet, ovarian aging is likely much greater than just a decline in estrogen. Indeed, ovarian aging involves a constellation of biological changes—*including rising levels of follicle-stimulating hormone (FSH) and dynamic alterations in the ovarian secretome*—that likely act in concert to affect target tissues and systems. FSH is not merely a passive biomarker of ovarian senescence; emerging

data suggest FSH may have direct or indirect roles in regulating adiposity, bone resorption and vascular tone. Likewise, the ovary continues to produce a range of hormones, peptides, and cytokines—many of which are not well-characterized—that may buffer or exacerbate the physiological effects of hormonal transitions.

Similar to estrogen, it is likely that secreted factors, *within the ovarian secretome*, have distinct molecular effects on local tissues (e.g., uterus) and distant systems (e.g., cardiovascular, skeletal, immune), influencing health trajectories in ways that are not yet well understood. A detailed characterization of how the secretome evolves during ovarian aging—*and its molecular crosstalk with other organ systems*—could yield unprecedented insights into the mechanisms of female-specific and female-predominant conditions. Whether use of menopausal hormone therapy (MHT) for the treatment of menopause alters gonadotrophin levels (e.g., FSH) and/or the ovarian secretome is poorly studied. Importantly, whether MHT, and different routes of administration of MHT, alter the ability of these mediators to molecularly impact local and distant tissues remains completely unknown. Thus, our ability to fully optimize female health is stagnated by our lack of understanding of the core biology that mediates health for women for most of their life.

To advance the science of female aging, it is imperative to reconceptualize the ovary not only as a reproductive organ but as a dynamic endocrine and paracrine hub whose aging contributes to systemic biological transitions. This shift in perspective has the potential to redefine diagnostic and therapeutic approaches, enabling targeted interventions that support longevity, prevent chronic disease and enhance quality of life for women across midlife and beyond.

Broad Research Priorities

Odessa is a targeted research effort designed to catalyze scientific progress in ovarian aging. We invite proposals for transformative, high-impact research and development efforts—*from discovery-stage science to technology validation and preclinical development*—focused on:

- Mapping the ovarian secretome across the premenopause, perimenopause and menopausal continuum utilizing well phenotyped cohorts of natural, surgical and hormonally modulated menopausal transitions
- Understanding the systemic effects of the ovarian secretome and interrogate potential modifiers or interrupters of these effects with a focus on sleep, metabolism, bone health, cognition and immunity
- Identifying actionable targets for extending health span and reducing both acute and long-term disease burden

Specific Research Priorities

We welcome both discovery-oriented investigations and translational efforts aimed at diagnostics, therapeutic target validation or intervention development. Cross-domain proposals and those integrating multi-omics, engineering, device development or drug discovery approaches are encouraged. Applicants must address at least one of the following domains.

Discovery and Validating the Ovarian Secretome Across the Lifespan

- Molecular profiling (e.g., proteomic, metabolomic, transcriptomic) of ovarian function and aging across the reproductive lifespan and menopause transition

- Identification and functional characterization of estrogen, estrogen-related and non-estrogenic bioactive factors produced by the ovary, including peptides, cytokines, microRNAs, metabolites and lipids
- Temporal mapping of secretome shifts in relation to systemic and local hormonal changes (e.g., FSH, AMH) during mid-life
- Exploring systemic biomarkers (e.g., blood, urine, saliva) that accurately reflect ovarian aging and can have utility as response to therapeutics
- Investigate tissue-of-origin mapping using cfRNA/cfDNA and/or EV-based biomarker panels targeting ovarian-derived vesicles

Ovarian aging and Female Health

- Revealing how clinically used MHT regimens (oral, transdermal, vaginal) modify hormonal profiles and the ovarian secretome and the impact of this response on clinical symptoms and conditions (e.g., osteopenia/osteoporosis; cognitive dysfunction, vasomotor symptoms)
- Studying the impact of ovarian aging on circadian rhythm, sleep disturbances and overall metabolic function; revealing the temporal relationship between ovarian aging, sleep disruptions, bone health and metabolic shifts
- Investigating the role of ovarian aging in insulin resistance, lipid metabolism and body composition shifts
- Investigating how ovarian aging intersects with the gut microbiome and microbiome-host interactions in driving symptomology of vasomotor symptoms, sleep and/or metabolic health
- Revealing how the factors in the ovarian secretome, including but not limited to estrogen, contribute to bone loss in the presence and absence of MHT; exploring interventions (e.g., physical, pharmacological, etc.) that modify these molecular responses
- Investigating direct mechanistic links between ovarian aging and immune dysfunction
- Investigate direct mechanistic links between ovarian aging and systemic aging as assessed by biological aging, epigenetic aging and/or other relevant physiological and molecular measures of accelerated aging
- Revealing how current therapeutics (e.g., MHT, SSRIs) and used but not yet rigorously studied therapeutics (e.g., GLP-1s) alter/improve short and long-term consequences of ovarian aging

Research Design Priorities

- Proposals from both academic and commercial entities are welcomed
- All proposals must contain a human component
- Human studies must include adequate sample sizes and appropriate metadata to support rigorous phenotyping
- Studies that do not have real time assessments of hormonal status but rely on recall bias or incomplete clinical records will not be considered responsive

- Traditional, clinically available hormone assessments must be included as comparators for any system biology approach to evaluating the ovarian secretome
- Studies that create well phenotyped biobanks are strongly encouraged
- Clinical trials are allowed but must collect biospecimens to uncover biological mechanisms underlying treatment response/non-response
- The use of biosensors, wearables and other technology, along with biosamples, to obtain more continuous physiological assessments are strongly encouraged
- Animal and *in vitro* models may be included but require strong justification demonstrating their translational relevance to human disease
- Non-human models should explicitly address whether relevant hormones are functional in the proposed model system (animal, cells, tissue, organoid)
- Use of models that do not accurately recapitulate the human condition or cannot be validated in humans are not considered responsive
- The use of existing biobanks and large datasets are allowed but must include ability to rigorously phenotype exposures and outcomes and account for impact of recall data and missing data
- Proposals from both academic and commercial entities are welcomed, individually and in collaborative efforts

Research that is not Considered Responsive

- Proposals with only non-human model systems and without a human component
- Research focused only on generalized aging processes
- Pure epidemiological studies
- Implementation studies
- Use of large databases without corresponding biological samples
- Use of large biobanks and datasets that lack adequate clinical data regarding use/timing and delivery of menopausal hormone therapy (MHT) or include participants that used MHT that is no longer clinical standard of care (e.g., medroxyprogesterone acetate) or do not have accurate information regarding time of menopause
- Studies comparing male and female aging

References and Resources for Odessa: Link