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Q1 Could you begin by telling us about your professional journey and how you first became interested in women's brain health and Alzheimer's disease?

My journey began when I was a postdoctoral fellow at The Rockefeller University, New York, USA. I had the remarkable opportunity to be a basic science observer on a clinical trial led by Howard M. Fillit, who was then an Assistant Professor and Associate Physician at Rockefeller, investigating the effects of oestrogen in women diagnosed with Alzheimer's disease.

There was a clear rationale for the study. Oestrogen promotes the activity of choline acetyltransferase, which generates acetylcholine. At that time, the degeneration of cholinergic neurons in the basal forebrain was one of the earliest recognised hallmarks of Alzheimer's pathology. These neurons produce acetylcholine, which is a neurotransmitter involved in learning and memory.

Through that trial, I came to know one of the participating women. She was an Adlerian psychologist and a wonderful storyteller. I would walk with her on the Rockefeller campus, and she would regale me with stories about the intellectual rivalries between Jung, Adler, and Freud.

One evening I walked her back to her room at the hospital. I bid her good night, closed the door, waited about 30 seconds, and then knocked and entered again. I asked her "Do you remember me?" Her reply was "I am so sorry, should I?"

In that moment, that one woman with Alzheimer's transformed this neuroscientist's journey. She could not remember me for 30 seconds, and I have remembered her for over 30 years.

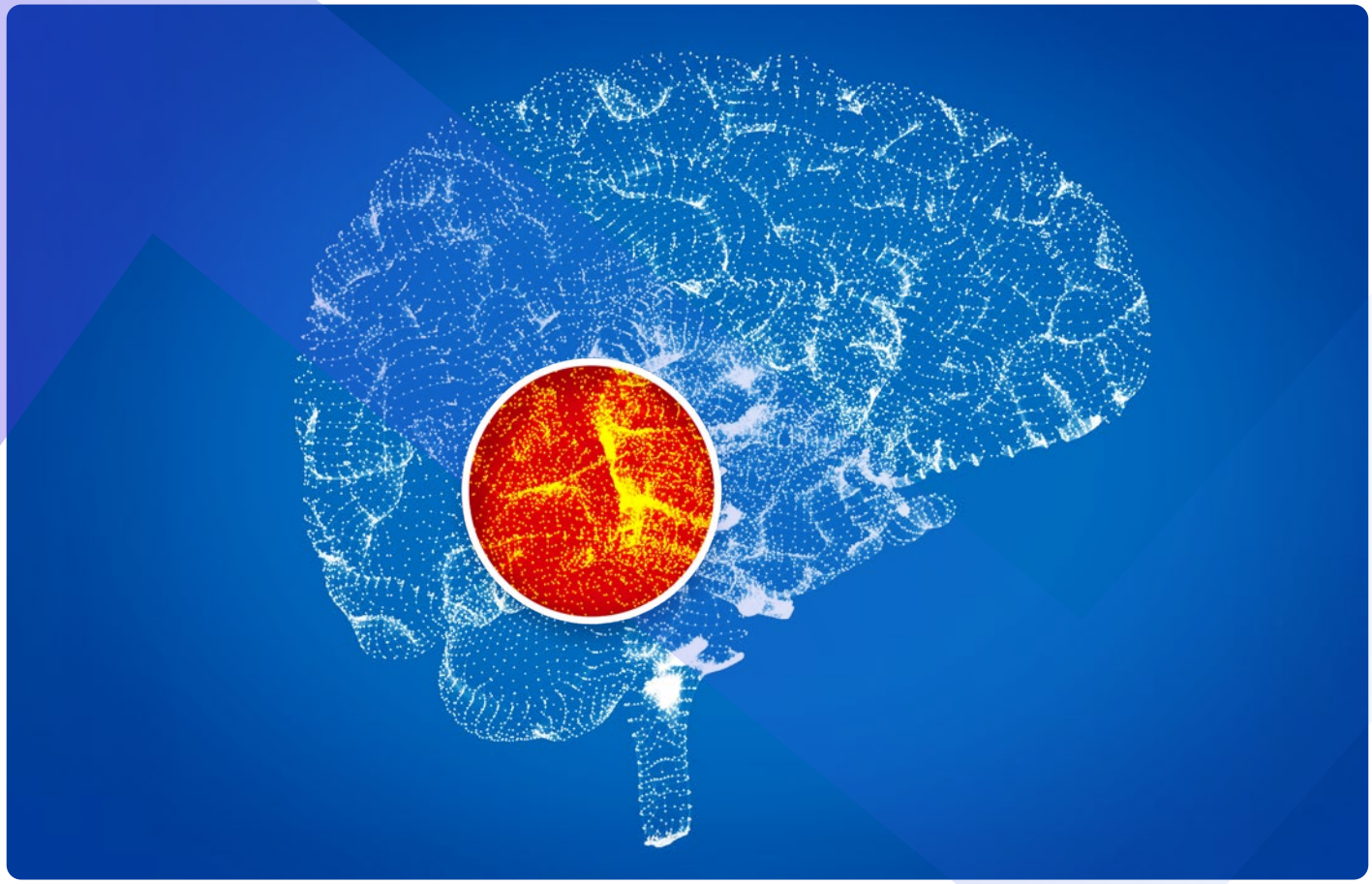
That moment changed the course of my scientific career and set me on a lifelong path to understand why women are at greater risk for Alzheimer's and to develop therapies that could prevent and even cure this disease.

Q2 You continue to attend meetings such as the International Society of Gynaecological Endocrinology (ISGE) Congress. What draws you to clinically focused meetings as a neuroscientist?

I come to ISGE for two broad reasons. First, the ISGE Congress is an opportunity to interact with clinicians. These are the people on the front lines of medicine. They are the ones making clinical decisions every day that affect women's health. Their knowledge and their challenges bring perspective that can inform our scientific research and our clinical trials. Medicine, especially around transitions such as menopause, is not linear. The complexity of human biology means that progress requires collaboration. None of us have all the answers.

Because of the interaction between scientists and clinicians, ISGE creates an innovative environment that encourages strategic innovative thinking and advances innovative solutions to challenges in women's health.

> **ISGE creates an innovative environment that encourages strategic innovative thinking**



Q3 Your research focuses on why women are disproportionately affected by Alzheimer's disease. Why is the female brain such an important area of investigation?

Two-thirds of all people living with Alzheimer's disease are women. If we want to prevent or treat this disease effectively, we must understand women's brain health.

Studying the female brain has revealed important biological insights, particularly around hormonal transitions such as the menopause. These transitions profoundly affect brain metabolism and neurological function. Interestingly, research in women has also advanced our understanding of the male brain. In men, testosterone can be converted to oestrogen within the brain. When testosterone production is suppressed, for example through certain medical treatments, the risk of Alzheimer's disease increases. Studying the female brain therefore helps illuminate broader mechanisms of brain ageing.

Q4 You mentioned a therapeutic currently being investigated in clinical trials. Could you describe the approach behind its development?

One of the therapeutics we are developing for Alzheiner's is based on allopregnanolone, a neurosteroid designed to stimulate regenerative mechanisms in the brain. This programme is currently in a Phase II clinical trial supported by the National Institute on Aging (NIA) within the National Institutes of Health (NIH).

More than 20 years ago, when we first proposed the idea of regenerating the Alzheimer's brain, regenerative medicine was not yet a well-established concept in neurology. Yet, the NIA supported the idea and encouraged us to pursue it.

Our goal is to activate the brain's intrinsic regenerative capacity. The Alzheimer's brain retains survival mechanisms that persist even as the disease progresses. If we can activate those mechanisms, we may be able to restore function.

Q5 Another area of your research involves PhytoSERM (NEUTherapeutics, Tucson, Arizona, USA). What is the concept behind this approach?

PhytoSERMs are plant-derived selective oestrogen receptor modulators designed to support both brain health and breast health.

Evidence suggests that menopausal hormone therapy can reduce the risk of Alzheimer's disease and other neurological conditions. However, many women hesitate to use hormone therapy because

of concerns about breast cancer. Instead of trying to persuade women to accept therapies they are uncomfortable with, we listened to those concerns.

Our research identified oestrogen receptor β as a particularly promising target. Activating this receptor in the brain promotes pathways associated with cognitive resilience, while in breast tissue it inhibits normal breast cell proliferation and also inhibits breast cancer cell proliferation and migration.

These two functions of oestrogen receptor β which is activated by PhytoSERMs has the potential to promote brain health while sustaining breast health. While our plan is to market PhytoSERM as an over-the-counter neutraceutical, we are developing PhytoSERM with all the scientific and clinical rigor of a pharmaceutical, because, in the end, our goal is provide women with an alternative that sustains brain health while protecting breast health.

Q6 Following the publication of the Women's Health Initiative, there was widespread concern about hormone therapy. How has our understanding evolved since then?

The Women's Health Initiative was conducted with rigorous scientific intent and a genuine concern for women's health. However, one critical factor was not fully understood: the impact of age on response to menopausal hormone therapy.

In that trial, hormone therapy was initiated in women in their 60s and 70's, long after the menopausal transition had occurred. We now understand that the brain undergoes substantial metabolic and inflammatory changes during menopause. Introducing hormone therapy after these processes are activated does not provide any benefit and in some women can induce harm.

Today, we recognise the importance of the timing hypothesis, which proposes that initiating hormone therapy closer to the menopausal transition may produce very different outcomes compared with starting treatment later. Science evolves through this process; each generation of research informs the next.

Q7 From a neuroscience perspective, how should clinicians think about hormone therapy and brain health?

If a woman is still experiencing menopausal symptoms such as hot flashes, she is likely still within the transition window where hormone therapy may have neurological benefits. However, once the transition has fully completed and symptoms have resolved, initiating hormone therapy purely for brain health becomes less clear.

This is where clinical expertise becomes critical. Every woman has a unique biological profile, including genetics, metabolic health, inflammation, and overall risk factors. We are actively working on creating the future of menopausal treatment by bringing precision medicine strategies to menopausal hormone therapy. Our goal is to provide women and their clinicians menopausal hormone therapy that is both personal and precise.

Q8 Some of your analyses have explored how managing multiple risk factors affects disease progression. What have these studies shown?

We analysed large datasets supported by the NIA, including the National Alzheimer's Coordinating Center and the Alzheimer's Disease Neuroimaging Initiative. We found that individuals who were receiving treatment for multiple Alzheimer's risk factors, including metabolic disease, hypertension, inflammation, and lipid dysregulation, experienced a delay of roughly 10 years in disease progression compared with those who were not receiving treatment. This did not cure Alzheimer's disease, but it significantly delayed the loss of independence. That additional decade of independent living is profoundly meaningful for patients and their families.

Q9 Looking ahead, how do you hope the conversation around menopause and brain health will evolve over the next decade?

In addition to their clinical assessments, physicians will have access to genetic data, metabolic biomarkers, and inflammatory profiles to guide treatment decisions. I believe the future lies in precision menopausal hormone therapy. Many different hormone formulations exist with different routes of administration. What we need now is the ability to match the right therapy to the right patient at the right time.

I return to the unique position that ISGE holds in the women's health space. ISGE brings together innovators from the scientific and clinical domains of women's health where they convene, challenge, and expand each other's knowledge and understanding. Ultimately, ISGE is creating an international innovation incubator to advance women's health across the lifespan.