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Q1 For most of its history, Parkinson's has been framed as a disease of dopamine loss in the brain, and treatment has followed that logic. You've increasingly argued that we need to look beyond the brain. What first convinced you that Parkinson's is a systemic disease?

For decades, we treated Parkinson's as if it were strictly an isolated issue in the substantia nigra. But if you actually sit in the clinic and listen to patients, you quickly realise the problem is located in multiple organs.

Long before a patient ever develops a tremor or stiffness, they routinely share stories of years spent dealing with constipation, sleep disturbances (like rapid eye movement sleep behaviour disorder), smell problems, and autonomic issues like orthostatic hypotension. Furthermore, when we look at pathology, we find misfolded α-synuclein aggregates distributed throughout the peripheral nervous system: in the skin, the colon, and the vagus nerve.

By the time motor symptoms appear, up to 50–70% of dopaminergic neurones in the brain are already gone. Realising this made it clear to me that Parkinson's is not merely a localised brain disease; it is a complex, systemic multi-organ syndrome. Treating it purely as a dopamine deficit in the brain is like trying to fix an entire electrical grid by replacing just one lightbulb.

"Parkinson's is not merely a localised brain disease; it is a complex, systemic multi-organ syndrome"

Q2 Your group has shown that misfolded α-synuclein can be found in the duodenum of patients, even early in the disease. How well does the gut-first versus brain-first picture actually hold up when you see patients, and what would it take for peripheral tissue to become a genuine diagnostic tool?

The 'gut-first versus brain-first' model holds up well in clinical practice, as it gives us a biological explanation for the vast heterogeneity we see in our patients.

Gut-first: these are the patients who present with early autonomic failure and sleep disorders years before motor symptoms surface. In these individuals, the pathology clearly starts in the enteric nervous system and ascends via the vagus nerve to the brainstem.

Brain-first: conversely, other patients present with classic asymmetrical motor symptoms first, with very little early autonomic disruption.

Our work identifying α-synuclein pathology and enteric gliosis in the duodenum of early-stage patients explicitly confirms this peripheral involvement. To turn peripheral tissue biopsies into a routine, everyday diagnostic tool, we need two things: standardisation and sensitivity. Techniques like seed amplification assays have revolutionised our ability to detect tiny amounts of misfolded proteins. If we can fully standardise skin biopsies or simple mucosal swabs so that any standard clinical pathology lab can replicate them reliably, we can transition peripheral tissue from a

research curiosity into a definitive diagnostic cornerstone.

Q3 You've drawn a comparison with cancer: that we should be trying to catch Parkinson's early, before significant neuronal loss. With skin biopsies and blood-based markers now emerging, are we close to diagnosing the disease before symptoms appear?

The cancer analogy is vital, because it challenges our current therapeutic passivity. In oncology, you don't wait for a tumour to metastasise and cause organ failure before you begin treatment. You screen, you find it at Stage 0 or 1, and you intervene. In Parkinson's, we have historically waited for the neurological equivalent of Stage 4, widespread neuronal death, before writing our first prescription.

Technologically, we are incredibly close to a pre-symptomatic diagnosis. The emergence of skin biopsies and blood-based biomarkers (such as checking for α-synuclein in neural extracellular vesicles or tracking neurofilament light chain) means we can now see the molecular signature of Parkinson's in the body years before the first tremor appears.

However, a diagnostic tool is only as useful as the actions it unlocks. Being able to predict who will get Parkinson's is a monumental scientific victory, but it creates an ethical and clinical dilemma if we do not have the disease-modifying therapies ready to deploy. The detection science is nearly there; now our therapeutics must catch up. The first Phase III studies with the monoclonal antibody prasinezumab are ongoing and hopefully will provide the first disease-modifying molecule for clinical use.

Q4 Advanced Parkinson's care still revolves largely around motor control, yet you've shown that non-motor symptoms drive much of the disability and loss of quality of life. Why have they remained so neglected, and what would it take to move them to the centre of treatment?

They have been neglected because they are largely invisible and difficult to quantify. A tremor is obvious; you can see it across the room, and you can measure it easily on a clinical scale. But you cannot easily 'see' a patient's cognitive slowdown, their crippling anxiety, their pain, or the fact that they have not slept through the night in years. Furthermore, motor symptoms respond well to early dopaminergic drugs, which created a historic bias toward focusing on what we could fix with a simple pill.

Moving non-motor symptoms to the centre requires a total paradigm shift in how we evaluate treatment success. Redefine 'outcomes': clinical trials must stop treating motor scores as the sole outcome. If a drug improves walking speed but worsens hallucinations or orthostatic hypotension, it is not a win for the patient.

Holistic management: we must actively use comprehensive tracking tools in daily practice.

Interestingly, advanced continuous drug delivery systems have shown us that when you stabilise the dopaminergic system continuously, many non-motor fluctuations improve as well. This proves that treating the whole person holistically helps across both motor and non-motor spectrums.

Q5 With deep brain stimulation, intestinal levodopa gel, apomorphine, and now subcutaneous infusions all available, how do you decide which patient needs which therapy when there are almost no head-to-head trials to lean on?

In the absence of massive head-to-head clinical trials, we have to look past the generic diagnosis and map the therapy to the patient's distinct clinical phenotype, cognitive status, and lifestyle.

To simplify this transition, I advocate for clear, simple, proactive screening protocols like the Making Informed Decisions to Aid Timely Management of Parkinson's Disease (MANAGE-PD) tool or the 5-to-1 rule: if a patient is taking oral levodopa five or more times a day, or has 2 hours of daily 'off-time', or 1 hour troublesome dyskinesia, it is time to stop tweaking oral medications and look at advanced options.

The selection then becomes highly individualised:

Deep brain stimulation: ideal for younger, cognitively sharp patients whose main challenges are severe tremors or motor fluctuations, and who are comfortable with neurosurgery.

Levodopa-carbidopa intestinal gel: highly effective for delivering absolute stability, but it requires a permanent percutaneous endoscopic gastrojejunostomy tube. This is excellent for patients who have reliable caregiver support and need robust, consistent delivery.

Continuous subcutaneous infusions: the newer subcutaneous levodopa/foslevodopa infusions represent a spectacular middle ground.

They offer the benefits of continuous dopaminergic stimulation without requiring invasive abdominal or brain surgery. This is a game changer for patients transitioning into the advanced stage who want to maintain autonomy without undergoing major procedures.

Q6 Looking ahead, what remains the most important unanswered question in Parkinson's for you?

We use the term 'Parkinson's disease' as if it is a single monolithic entity, but it isn't. It is an umbrella term for a collection of different biological pathways that happen to share a final common path of motor symptoms. A patient with a *GBA* mutation behaves differently from someone with a *LRRK2* mutation, who behaves differently from a patient who is 'gut-first', presenting with early dementia.

Until we can precisely map a patient's exact biological endophenotype, our clinical trials for disease-modifying therapies continue to struggle. The challenge is how to create a flawless system of precision medicine for Parkinson's, one where we can identify the biological subtype of the individual and match it immediately to a targeted therapy before a significant number of brain cells are lost.