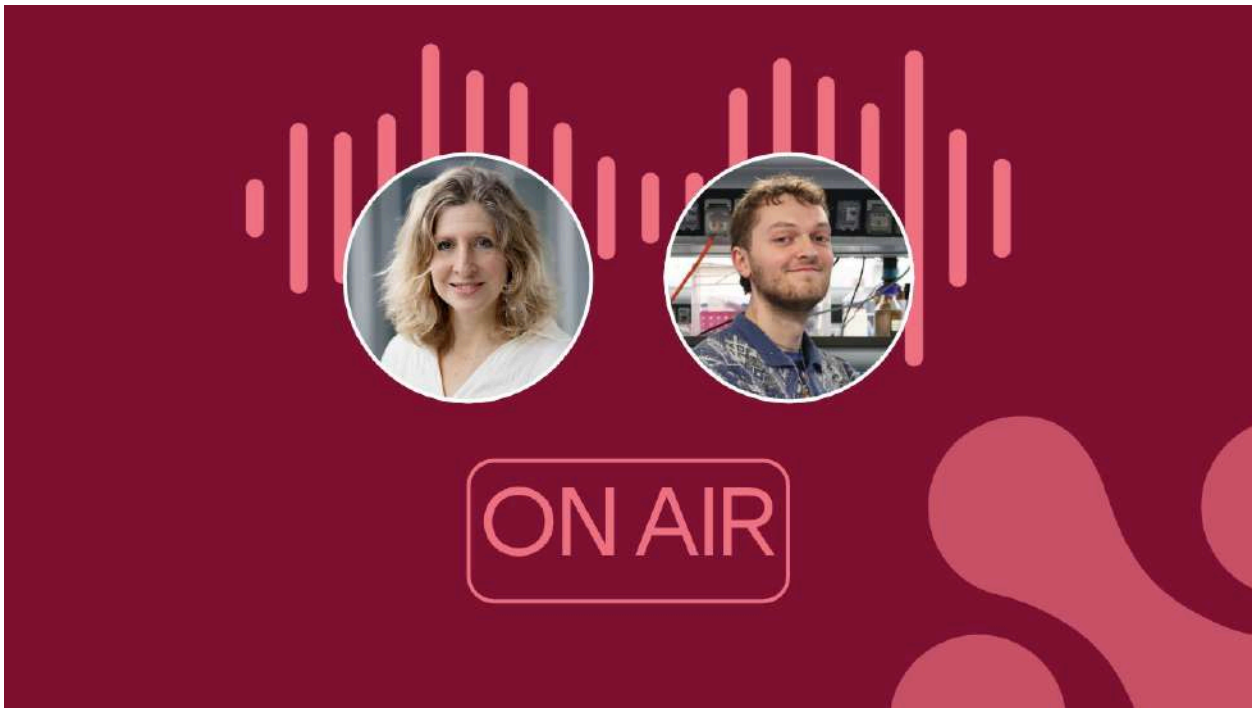
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menTOR Voices #2 — Lab Showcase: Dr. Stéphanie Baulac and Lucas van Endert

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Welcome to the second issue of menTOR Voices! Through this monthly series, we take you inside the laboratories, science, and people shaping the menTOR MSCA Doctoral Network.

For our second edition, we feature Stéphanie Baulac[1] (Research Director, Inserm, from the Paris Brain Institute - ICM) and her student Lucas van Endert (doctoral candidate in the menTOR Doctoral Network). Together, we discuss their research on somatic mosaicism in focal epilepsies, spatial transcriptomics on resected human brain tissue, the origins of the network from TOR de France, and the multidisciplinary training of early-career researchers.



Unraveling somatic mosaicism in focal cortical epilepsies

Jean M. Grangeon — Could you introduce your laboratory's research theme and explain how you first entered the mTOR field and connected with Mario Pende[2]?

Stéphanie Baulac — Our research focus centers on the genetics of neurodevelopmental focal epilepsies at the Paris Brain Institute. In our work on focal cortical dysplasia, we investigated why seizures originate locally in specific brain regions. This focal and

mosaic pattern at histology led us to hypothesize that genetic variants are present in all cells, nor inherited from parents, but rather arise spontaneously during embryonic neurodevelopment, and there present in only a subset of cells.

This phenomenon is known as somatic mosaicism: the brain becomes a mosaic composed of normal cells surrounded by a small fraction of mutated cells.

In focal cortical dysplasia type II[3], these somatic variants occur within key regulatory genes of the mTOR pathway—notably DEPDC5 a key component of the GATOR1[4] complex, which acts as a crucial brake on mTOR signaling.

Even a small percentage of mutated dysmorphic cells is sufficient to trigger seizures across the brain. Connecting with Mario Pende and joining forces allowed us to build an interdisciplinary framework bridging basic mTOR biology, genetics, and clinical neuropathology.

Spatial transcriptomics on resected human brain tissue

J.M.G. — Lucas, you joined Stéphanie Baulac's laboratory a year ago as a doctoral candidate within the menTOR Doctoral Network. What are the core goals and methodological approaches of your PhD project?

Lucas van Endert — The central goal of my PhD project is to decipher the precise pathogenic mechanisms connecting mTOR pathway hyperactivation in dysmorphic neurons[5] to epileptic seizure activity. Patients with focal cortical dysplasia type II exhibit characteristic histopathological features, such as cytomegalic dysmorphic neurons[6] and balloon cells. While previous work in our laboratory demonstrated a causal link between dysmorphic neurons and seizure generation, the precise downstream molecular mechanisms remain unknown.



Lucas van Endert — MSCA PhD Fellow | menTOR Doctoral Network

To address this, we take advantage of a direct translational pipeline using fresh human brain tissue resected during surgery from patients with drug-resistant focal epilepsy.

J.M.G. — How do you combine electrophysiology and spatial transcriptomics on these clinical samples?

L.v.E. — When tissue arrives directly from surgery, our collaborator Mélina Scopin (a PhD student in Jean-Christophe Poncer's team[7]) performs *ex vivo* electrophysiological recordings to locate foci of pseudo-epileptic activity. We then freeze those exact tissue samples to perform spatial transcriptomics[8]. This technology allows us to capture single-cell gene expression profiles while preserving spatial coordinates within the tissue architecture.

By overlaying spatial electrical recordings with transcriptomic maps, we aim to identify candidate genes deregulated downstream of mTOR in dysmorphic neurons or their surrounding microenvironment. In parallel, our lab uses human cortical organoid models with inducible mutations to track earlier developmental stages.

From TOR de France to the menTOR Doctoral Network

J.M.G. — Stéphanie, how does the international TOR de France network relate to the European MSCA Doctoral Network menTOR?

S.B. — TOR de France is the founding community. Its primary mission is to bring together researchers, clinicians, and specialists across France and Europe through regular conferences and scientific exchanges.

Because mTOR acts as a universal metabolic hub present in all cell types, mutations in this pathway drive diverse human pathologies ranging from neurological disorders to cancers and metabolic diseases. The menTOR Doctoral Network represents the structured European PhD training arm of this ecosystem, enabling multi-laboratory collaborations, secondments, and joint training events across academic institutions and industrial partners.

The multidisciplinary power of European doctoral training

J.M.G. — Lucas, how does participating in an international European doctoral network impact your daily PhD experience?

L.v.E. — It is a major strength. During menTOR summer schools—such as the first school in Tübingen focusing on drug discovery and the second in Naples on metabolic regulation—we are exposed to fields outside our daily focus.

Interacting with PhD candidates working on cell biology, structural biophysics, or metabolism provides fresh perspectives and new ideas that directly enrich my own project.

J.M.G. — menTOR's students also lead communication initiatives within the network?

L.v.E. — Yes. Together with Alisa K. - Alisa Kirkin - (a PhD candidate in Claudio De Virgilio's lab[9]), we manage monthly scientific literature selections and publication highlights on LinkedIn. We are also working with our doctoral student group to establish regular paper discussions and journal clubs across the network.

Future horizons and targeted therapeutics for mTORopathies

J.M.G. — What are the key long-term therapeutic perspectives for patients affected by mTORopathies?

S. B. — Because mTOR regulates fundamental cell growth across the entire body, global inhibition carries limitations. Our therapeutic objective is to identify specific biomarkers of mutated, hyperactive brain cells to selectively target diseased cells without disrupting physiological mTOR signaling in normal cells.

J.M.G. — What enduring legacy do you hope the menTOR network leaves for European science?

L.v.E. — Beyond scientific discoveries, the network's greatest legacy will be establishing a lasting, interconnected community of early-career scientists across Europe who can seamlessly bridge fundamental biology, clinical translation, and industrial drug discovery.

References

[1] Brain Mosaicism in Epilepsy and Neurodevelopmental Disorders: Paris Brain Institute - ICM

[2] Cell Growth Control by Nutrients: Institut Necker Enfants Malades

[3] Focal Cortical Dysplasia (Type II): a localized neurodevelopmental malformation of the brain's outer layer (cortex). "Focal" indicates that the lesion is restricted to a small area in one brain hemisphere, while "Type II" is specifically characterized by abnormal, severely enlarged brain cells (dysmorphic neurons and balloon cells) that provoke drug-resistant epileptic seizures.

[4] GATOR1 complex and DEPDC5: GATOR1 is a key protein complex (which includes the protein encoded by the DEPDC5 gene) that functions as a natural "brake" on the mTOR pathway. When mutations disable GATOR1 or DEPDC5, this natural brake is lost, leading to continuous mTOR hyperactivation and abnormal cell enlargement in the developing brain.

[5] Dysmorphic neurons and balloon cells: distinctive, giant, abnormal cells found within dysplastic brain tissue. Dysmorphic neurons are abnormally large, misshapen nerve cells with altered internal structures, while balloon cells are giant, immature cells. Together, these aberrant cells act as the spark plug that generates epileptic activity.

[6] Cytomegalic neurons: abnormally enlarged brain cells resulting from hyperactive mTOR signaling, a hallmark neuropathological feature of focal cortical dysplasia type II.

[7] EpiC: Clinical and experimental epilepsy, the Paris Brain Institute - ICM

[8] Spatial transcriptomics: a cutting-edge molecular profiling technology that measures which genes are turned "on" or "off" in individual cells while preserving their exact physical 2D/3D location within the brain tissue slice. This enables scientists to map gene activity directly onto real-time electrical recording maps.

[9] The Molecular Architecture of Nutrient Sensing: Université de Fribourg



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The menTOR Doctoral Network investigates the mTOR signaling hub — a central regulator of cellular growth and metabolism. Aberrant mTOR activity drives major age-related diseases (cancer, obesity, diabetes) as well as rare genetic mTORopathies. Bringing together leading European partners, menTOR trains 18 Doctoral Candidates to decode these mechanisms, advance personalized medicine, and open new therapeutic avenues.

🌐 Explore our network and research: mentor-program.eu

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Credits

Editorial direction: Mario Pende

Editor-in-chief and art direction: Jean M. GRANGEON for KOM Agency

Photography: Studio Cassanas, Adrien Schramm

This project has received funding from the European Union's Horizon Europe research and innovation programme under the Marie Skłodowska-Curie grant agreement No 101168624.