Master 2 Reproduction et Développement
Stage de recherche 2024-2025

Stage proposé par

Nom et adresse du Laboratoire ou de l'Unité : Diseases and Hormones of the Nervous System, Inserm U1195, UPSaclay, Hôpital de Bicêtre, 80 rue du Général Leclerc, 94276 Le Kremlin-Bicêtre

Téléphone : 0149595386
Mail : christian.specht@inserm.fr
Site internet : https://dhns-inserm.fr/
Directeur du Laboratoire ou de l'Unité : Michael Schumacher

Intitulé de l 'équipe d'accueil : Système nerveux central et neurostéroïdes

Prénom et NOM du Responsable de l'équipe : Michael Schumacher

Résumé du thème de recherche de l'équipe (une dizaine de lignes maximum)
L'équipe se concentre sur l'identification de nouvelles approches thérapeutiques destinées au traitement des maladies du système nerveux dont les protéinopathies. Nous étudions les mécanismes associés ainsi que les thérapies potentielles pour prévenir ou guérir ces maladies, en nous concentrant sur trois pathologies : i. La neuropathie périphérique causée par la transthyrétine amyloïdogène ; ii. les maladies associées aux protéines bêta-amyloïde et tau (maladie d'Alzheimer, démence fronto-temporale) ; iii. Maladies associées à l'alpha-synucléine (maladie de Parkinson, maladie à corps de Lewy).

Titre du projet de stage :

Exploring the disease mechanism of Parkinson disease using super-resolution microscopy

Prénom, NOM, téléphone et adresse e-mail du Responsable du stage:
Christian SPECHT, 0149595386, christian.specht@inserm.fr

Projet de stage : (une vingtaine de lignes maximum)

The protein alpha-synuclein is widely expressed in the central nervous system. Located in synapses, it is thought to modulate the transmission of electrical signals between neurons, but its exact function is not known. In pathological conditions, alpha-synuclein becomes misfolded, and forms intracellular deposits called Lewy neurites and Lewy bodies (https://doi.org/10.3389/fnsyn.2020.584536). These fibrillar forms of alpha-synuclein are toxic to neurons and eventually lead to their death. Alpha-synuclein fibrils are also released from damaged neurons and can enter other neurons, spreading the toxicity throughout the central nervous system. This pathological process occurs in several neurodegenerative diseases known as alpha-synucleinopathies, including Parkinson disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA).

Two important questions about the mechanism of alpha-synuclein pathologies will be addressed in this project. First, what is the pathway by which alpha-synuclein fibrils are transmitted between neurons? Second, what are the effects of alpha-synuclein pathology on synaptic structure and function? To study these issues, we will use Single Molecule Localisation Microscopy (SMLM), a 2014 Nobel Prize-winning super-resolution technique based on the detection of individual fluorescent proteins with nanometer resolution (https://doi.org/10.1016/j.tcb.2022.06.011). This allows us to study the precise mechanisms by which exogenous fibrils of alpha-synuclein are internalised and the downstream consequences inside the affected neurons. The dynamics of alpha-synuclein in axons and at synapses will be studied in control and pathogenic conditions by SMLM, in order to trace the earliest stages of the pathogenic process. Our project will thus provide a better understanding of the degenerative process in PD and other alpha-synucleinopathies, and lead to possible therapeutic solutions (https://doi.org/10.3389/fnsyn.2021.753462).

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Techniques mises en œuvre par le stagiaire :
The M2 student will learn hands-on skills in cutting-edge imaging techniques including confocal microscopy, SMLM, and correlative light and electron microscopy CLEM, as well as a range of cellular and molecular biology methods (neuron culture, virus expression, histology and immunocytochemistry). The M2 candidate will be supervised by researchers and technical staff and participate in labmeetings and seminars. Advanced imaging equipment is available at the host laboratory, including a Zeiss Elyra PS1 microscope for super-resolution imaging and a new state-of-the-art Abbelight SAFe 360 nanoscope for 3D and multi-colour SMLM in living and fixed neurons and brain slices. The laboratory also has cell culture rooms, an animal facility, and shared infrastructure for confocal microscopy, EM, biochemistry and molecular biology, work benches and office space.

Publications du Responsable de stage au cours des 5 dernières années (*sélection*) :

Wiessler AL, Hasenmüller AS, Fuhl I, Mille C, Campo OC, Reinhard N, Schenk J, Heinze KG, Schaefer N, Specht CG*, Villmann C* (2024). Role of the glycine receptor ß subunit in synaptic localization and pathogenicity in severe startle disease. **J Neurosci** 44:e0837232023.

Cabriel C, Monfort T, Specht CG, Izeddin I (2023). Event-based vision sensor for fast and dense single-molecule localization microscopy. **Nat Photon** 17:1105–1113.

Verdier H*, Laurent F, Cassé A, Vestergaard CL, Specht CG*, Masson JB* (2023). Simulation-based inference for non-parametric statistical comparison of biomolecule dynamics. **PLoS Comput Biol** 19:e1010088.

Khayenko V, Schulte C, Reis SL, Avraham O, Schietroma C, Worschech R, Nordblom NF, Kachler S, Villmann C, Heinze KG, Schlosser A, Schueler-Furman O, Tovote P, Specht CG*, Maric HM* (2022). A versatile synthetic affinity probe reveals inhibitory synapse ultrastructure and brain connectivity. **Angew Chem** 61:e202202078.

Specht CG* (2021). A quantitative perspective of alpha-synuclein dynamics – why numbers matter. **Front Syn Neurosci** 13:753462, https://doi.org/10.3389/fnsyn.2021.753462

Maynard SA, Rostaing P, Schaefer N, Gemin O, Candat A, Dumoulin A, Villmann C, Triller A*, Specht CG* (2021). Identification of a stereotypic molecular arrangement of endogenous glycine receptors at spinal cord synapses. **Elife** 10:e74441.

Yang X, Le Corronc H, Legendre P, Triller A*, Specht CG* (2021). Differential regulation of glycinergic and GABAergic nanocolumns at mixed inhibitory synapses. **EMBO Rep** 22:e52154.

Chapdelaine T, Hakim V, Triller A, Ranft J*, Specht CG* (2021). Reciprocal stabilisation of glycine receptors and gephyrin scaffold proteins at inhibitory synapses. **Biophys J** 120:805-817.

Specht CG* (2020). Fractional occupancy of synaptic binding sites and the molecular plasticity of inhibitory synapses. **Neuropharmacol**, 169:107493.

Autres informations :

Etudiants actuellement en thèse ou en M2 dans l'équipe d'accueil.

Année de début	Doctorant(e)	Directeur	Status / ED
2021	Adil El Mesaoudi	Elisabeth Traiffort	PhD Biosigne
2022	Ying Ding	Shixin Ye-Lehmann	PhD Biosigne / CSC
2022	Océane Hage	Marcel Tawk	PhD Biosigne
2023	Marianne Bardy-Lagarde	Abdel Ghoumari	PhD Biosigne
2023	Dalya Gulseren	Specht / Kabani	M2

Etudiants ayant préparé ou soutenu leur thèse ou leur M2 dans l'équipe d'accueil au cours des six dernières années.

Durée	Doctorant(e)	Directeur	ED	Devenir
2018-2021	A. Kassoussi	E. Traiffort	Biosigne	Postdoc
2018-2022	YuTing Liu	C. Specht	ED3C	Research scientist (Biogen)
2019-2022	Amina Zahaf	E. Traiffort	Biosigne	Postdoc

Stage ouvert à tous les profils ? *Oui*
Ce sujet peut-il donner lieu à une thèse ? *La poursuite d'une thèse est fortement encouragée.*