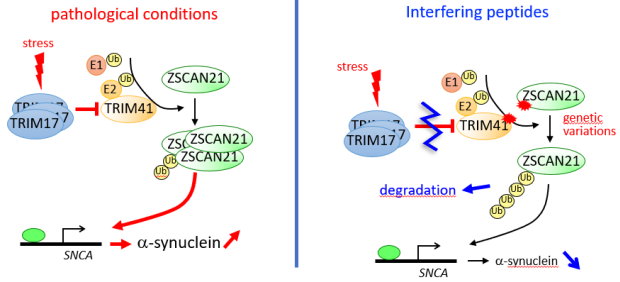


## 2027 Internship Offer

**Master 1:** YES – Duration: 2 month

**Master 2:** YES – Duration: 6 month

Team, Contact	Thierry Forné lab, Supervisor Irena Lassot: irena.lassot@igmm.cnrs.fr
Title	Modulation of alpha-synuclein expression as a potential therapeutic target in Parkinson's disease
Research Themes and questions	<p>Accumulating data indicate that even a limited increase in wild-type <math>\alpha</math>-synuclein (<math>\alpha</math>syn) expression can cause both familial and sporadic forms of Parkinson's disease (PD). We have identified a pathway regulating <math>\alpha</math>syn expression in which TRIM41 mediates the degradation of the transcription factor ZSCAN21 while TRIM17 stabilizes it by inhibiting TRIM41. Silencing ZSCAN21 or TRIM17 prevents both transcriptional induction of <math>\alpha</math>syn and neurodegeneration in PD models. Furthermore, we identified in familial PD cases variants in ZSCAN21 and TRIM41 genes resulting in ZSCAN21 accumulation and increased <math>\alpha</math>syn expression. Therefore, our data strongly suggest that this pathway play a crucial role in the transcriptional induction of <math>\alpha</math>syn that causes PD. Our goal is to modulate this pathway using interfering peptides to enhance ZSCAN21 degradation and restore levels of <math>\alpha</math>syn that are compatible with neuronal survival in order to halt the progression of the disease.</p>
Methods and experimental approaches	<p>Various experimental approaches <i>in vitro</i> and in cells (2 different models of Parkinson's disease) to validate peptide/protein interactions and the inhibitory effects of peptides (recombinant proteins or proteins overexpressed in cells) using co-immunoprecipitation and TSA (thermal shift assay). RTqPCR or digital PCR on total RNA or chromatin-RNA to see the effects of peptides on <math>\alpha</math>syn expression in cellular models of the disease.</p>
Illustration	 <p>The diagram is split into two panels: 'pathological conditions' (left) and 'Interfering peptides' (right).  <b>Pathological conditions:</b> Stress (red lightning bolt) activates TRIM17 (blue circle). TRIM17 inhibits TRIM41 (red circle). TRIM41 normally targets ZSCAN21 (green oval) for ubiquitination (Ub, yellow circles) and degradation. In pathological conditions, TRIM41 is inhibited, leading to ZSCAN21 accumulation. This accumulation, along with genetic variations (red lightning bolt), leads to increased transcription of the SNCA gene (green box), resulting in increased alpha-synuclein expression (red arrow).  <b>Interfering peptides:</b> Stress activates TRIM17. Interfering peptides (blue lightning bolt) inhibit TRIM17, which in turn allows TRIM41 to function normally. TRIM41 targets ZSCAN21 for degradation. This leads to ZSCAN21 depletion, which reduces SNCA transcription and alpha-synuclein expression (blue arrow).</p>
2-3 Publications	<ul style="list-style-type: none"> <li>- Kozoriz A, et al., <i>Cell Death Dis.</i> 2025 May 16;16(1):394.</li> <li>- Basu-Shrivastava M, et al., <i>Cells</i> 10: 1235 (2021).</li> <li>- LASSOT I. et al., <i>Cell reports</i> 25: 2484-2496.e9. (2018).</li> </ul>