Abstract for IAS Symposium on Frontiers in Neuroscience (June 16-19, 2025)

Decoding Gene Regulation During CNS Repair

Enric Llorens-Bobadilla

Department of Cell and Molecular Biology, Karolinska Institutet, Sweden

Email: enric.llorens@ki.se

Central nervous system (CNS) injury presents enduring challenges due to limited intrinsic repair. Through integrative single-cell and spatial multi-omics approaches, we have uncovered fundamental mechanisms governing glial cell plasticity that can be exploited for tissue regeneration. Our analyses reveal that glial cells, including neural stem cells and astrocytes, possess remarkable regenerative potential encoded within their chromatin architecture and enhancer landscapes. Neural stem cells maintain a permissive chromatin state that enables activation of latent oligodendrogenic programs following injury, which can be redirected through transcription factor manipulation. Concurrently, we have mapped the injury-responsive enhancer elements that coordinate cell state-specific gene expression across glial populations at lesion borders. These enhancers integrate general stress response mechanisms with glial subtype-specific factors, allowing precise transcriptional control during repair processes. Our studies reveal two complementary approaches to harness glial plasticity: first, exploiting the permissive chromatin landscape in neural stem cells through ectopic developmental transcription factor expression triggers robust oligodendrogenesis and redirects the glial response toward regeneration rather than scarring; second, decoding the architecture of injury-induced enhancers enables the design of programmable gene therapy vectors that selectively target reactive glial populations at lesion sites. Our ongoing investigations further explore additional transcriptional networks that may facilitate glial-mediated repair through systematic screening and integrative genomic analyses, potentially unlocking new regenerative capacities within the injured CNS.

References:

[1] Llorens-Bobadilla, E., Chell, J.M., Le Merre, P., Wu, Y., Zamboni, M., Bergenstråhle, J., Stenudd, M., Sopova, E., Lundeberg, J., Shupliakov, O., Carlén, M. and Frisén, J. (2020) A latent lineage potential in resident neural stem cells enables spinal cord repair. Science, 370, eabb8795.

[2] Llorens-Bobadilla, E.#, Zamboni, M., Marklund, M., Bhalla, N., Chen, X., Hartman, J., Frisén, J., and Ståhl. P.L.# (2023). Solid-phase capture and profiling of open chromatin by spatial ATAC. Nature Biotechnology, 41(8), 1085-1088.