Exploring the retinoids-driven gene regulatory programs implicated on the "morpho-space architecture" leading to nervous tissue formation

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Developmental processes – describing how organisms are formed in a spatio-temporal context - were historically studied at tissue (morphogenesis) and cellular levels (cell proliferation and specialization), but also by discovering molecular entities that form concentration gradients in a spatio-temporal fashion (morphogen gradients). Among all these levels of granularity, morphogens were early on shown to be able to control both cell specialization and tissue organization, hence providing a mechanistic view of the events controlling morphogenesis [1].

Retinoic Acid (RA) is a key morphogen during vertebrate embryogenesis, including the development of the nervous system [2,3]. RA action is mediated by binding to RAR/RXR retinoid receptor heterodimers, which act as ligand-dependent transcription factors[4]. Each of the RAR and RXR heterodimer components are expressed as three isotypes (α, β, γ), thus diversifying the initial cue by regulating multiple cognate gene regulatory programs (GRPs) by sets of RAR/RXR heterodimers. In fact, previous studies demonstrated that different heterodimers regulate distinct gene targets, further supported by the capacity of RAR-specific agonists to mimic the differentiation phenotype induced by the pan-RAR/RXR agonist, all-*trans* retinoic acid [5–8]. A large number of specific retinoids and rexinoids presenting agonist/antagonist capacities has been generated, thus facilitating the dissection of the contribution of RAR isotypes and of the heterodimer partners to regulated biological phenomena[5].

Our previous work performed with RA-driven endodermal[6], and more recently on neuronal precursors[7], provided a detailed view of the major GRPs initiated by RAR/RXR to induce a given cell fate. These studies demonstrated that it is possible to reconstruct RA-triggered gene regulatory programs (GRPs) by integrating temporally collected omics readouts by *in silico* modelling of the signaling cascade.

The proposed project aims at expanding our previous studies to a detailed characterization of the gene regulatory wires involved in nervous tissue formation, form the angle of the role of the various RAR/RXR driven programs. Specifically, the student will setup neuronal differentiation assays from human induced pluripotent stem cells and explore the role of synthetic RAR agonists for directing this process. In addition, he/she will expand this effort to the use of 3-dimensional cerebral organoid cultures as a way to count for a more complex differentiation system. Modern function genomics readouts will be used for tracking cell differentiation, including single-cell and Spatial transcriptomics profiling, but also Cut&run / Cut&tag methodologies for mapping the RAR/RXR binding landscapes.

PhD students' profile and skills required:

The candidate (F/M) must hold a Master 2 and have acquired skills in at least two of the following fields: cell biology, stem cells, neurobiology, molecular biology. Basic knowledge in functional genomics and/or bioinformatics and/or systems biology are an asset. She / he should preferably have acquired technical skills in cell culture of eukaryotic cells and in molecular biology.

Our team is located at the Unit Génomique Métabolique (UMR 8030); Genoscope; Evry; France. For further information, please contact us at the following address:

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Bibliography

1. Sagner, A. & Briscoe, J. Morphogen interpretation: concentration, time, competence, and signaling dynamics. *Wiley Interdisciplinary Reviews: Developmental Biology* **6**, e271 (2017).
2. Rhinn, M. & Dollé, P. Retinoic acid signalling during development. *Development* **139**, 843–858 (2012).
3. Maden, M. Retinoic acid in the development, regeneration and maintenance of the nervous system. *Nat. Rev. Neurosci.* **8**, 755–765 (2007).
4. Gronemeyer, H., Gustafsson, J.-A. & Laudet, V. Principles for modulation of the nuclear receptor superfamily. *Nat Rev Drug Discov* **3**, 950–964 (2004).
5. Álvarez, R., Vaz, B., Gronemeyer, H. & de Lera, Á. R. Functions, therapeutic applications, and synthesis of retinoids and carotenoids. *Chem Rev* **114**, 1–125 (2014).
6. Mendoza-Parra, M. A., Walia, M., Sankar, M. & Gronemeyer, H. Dissecting the retinoid-induced differentiation of F9 embryonal stem cells by integrative genomics. *Mol. Syst. Biol.* **7**, 538 (2011).
7. Mendoza-Parra, M.-A. *et al.* Reconstructed cell fate-regulatory programs in stem cells reveal hierarchies and key factors of neurogenesis. *Genome Res.* **26**, 1505–1519 (2016).
8. Cholley, P.-E. *et al.* Modeling gene-regulatory networks to describe cell fate transitions and predict master regulators. *npj Systems Biology and Applications* **4**, 29 (2018).