Master 2 Reproduction et Développement
Stage de recherche 2024-2025

Stage proposé par :

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Intitulé de l'équipe d'accueil : *'Empreinte Génomique et Développement'*

Prénom et NOM du Responsable de l'équipe : Dr. Robert FEIL

Résumé du thème de recherche de l'équipe

Our team is interested in epigenetics. We explore the epigenetic phenomenon of genomic imprinting and why this is important for development and human disease. We use the mouse as a model system, and study important imprinted domains in naïve embryonic stem cells (ESCs) and in ESC-derived neural and mesodermal cells. A main question is how at imprinted gene domains, the 'imprinting control regions' (ICRs) brings about the mono-allelic expression of nearby genes during development. We find that this process involves covalent chromatin modifications and chromatin compaction. At some loci, it requires the expression of imprinted long non-coding RNAs (lncRNAs). We functionally explore several imprinted lncRNAs in our lab. In a linked second theme, we unravel in detail the structural organization of imprinted gene domains and whether this is influenced by lncRNAs as well.

Titre du projet de stage :

The imprinted lncRNA Meg3 in developmental gene regulation and stress responses.

Prénom, NOM, téléphone et adresse e-mail du Responsable du stage:

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Projet de stage :
Genomic imprinting plays is an epigenetic phenomenon that plays diverse roles in development, homeostasis and behavior. Its perturbation causes congenital diseases and often occurs in cancer as well. Our lab has used the imprinted *Dlk1-Dio3* domain on mouse chromosome 12 as a paradigm for addressing the regulation and role of genomic imprinting, and how its epigenetic perturbation induces different complex diseases. This large chromosomal domain comprises the developmental *Dlk1* and *Rtl1* genes, which are both repressed on the maternal chromosome. On this parental chromosome, the domain's intergenic 'imprinting control region' activates in *cis* a large polycistron that produces the lncRNA Meg3 and also many miRNAs and snoRNAs. Recently, we found that Meg3 lncRNA is focally retained on the locus on the maternal chromosome, and that this important for the allelic repression of *Dlk1* and *Rtl1*. How precisely this all works, and whether Meg3 could act as a scaffold to tether specific proteins to target genes, remains unclear. Meg3 lncRNA has diverse poorly understood roles in *trans* as well, including the activation of specific p53 target genes. Using normal diverse CRISPR-modified hybrid ES cell systems, this MII project will further explore the action and role of the lncMeg3 during stem cell differentiation. Various functional assays used routinely in the lab will be performed on cell lines with altered Meg3 expression. Findings may be relevant for understanding the involvement of Meg3 in development and in specific human diseases.

Techniques mises en œuvre par le stagiaire :
-Culture and differentiation of primary mouse cells (ESCs, NPCs).
-Transformation and cell clone derivation.
-Gene expression studies.
-Fluorescence *in situ* hybridization.
-Data analysis and documentation.

Publications du Responsable de stage au cours des 5 dernières années (*, auteur correspondant):

Farhadova S, Ghousein A, Charon F, Surcis C, Gomez-Velazques M, Roidor C, Di Michele F., Borensztein M., De Sario A, Noordermeer M, Moindrot B*, Feil R* (2024). Meg3 lncRNA mediates imprinted gene expression during stem cell differentiation. ***Nucleic Acids Res***, April, gkae247.

Moindrot B., Imaizumi Y, Feil R* (2024). Differential 3D genome architecture and imprinted gene expression: cause or consequence? ***Biochem Society Transactions,*** in the press.

Dupont, C., Chahar, D., Trullo, A., Gostan, T., Fisher, D., Feil, R.*, Llères, D.* (2023). FRET-based microscopy reveals limited compaction of heterochromatin in living embryonic stem cells. ***EMBO J.,*** e110286.

Di Michele, F., Chillon, I, Feil, R.* (2023). Imprinted lncRNAs in mammalian development and disease. ***Int. J. Mol. Sci.,*** 24 :13647.

Esnault, C., Magat, T., El Aabidine, A.Z., Garcia-Oliver, E., Cucchiarini, A., Bouchouika, S., Llères, D., Goerke, L., Luo, Y., Verga, D., Lacroix, L., Feil, R., Spicuglia, S., Mergny J-L., Andrau, J-C. (2023). G4access reveals G-quadruplexes associate to open chromatin and to imprinting control regions. ***Nature Genetics***, 55:1359-1369.

Llères, D, Imaizumi, Y., Feil, R. (2021). Exploring chromatin structural roles of non-coding RNAs at imprinted domains. ***Biochem Society Transactions***, 49, 1867-1879.

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Acursio, B., Verma, A., Polito, A., Giaccari, C., Cecere, F., Fioriniello, F., Della Ragiona, F., Fico, A., Angelini, C., Feil, R., Riccio, A. (2021). *Zfp57* inactivation illustrates the role of ICR methylation in imprinted gene expression during neural differentiation of mouse ESCs. ***Scientific reports*****,** 11, 13802.

Herbette, M., Robert, V., Bailly, A., Gely, L., Feil, R., Llères, D., Palladino, F (2020). A role for *Caenorhabditis elegans* COMPASS in germline chromatin organization. ***Cells*****,** 9 (9), E2049.

Noordermeer, D.*, Feil, R.* (2020). Differential chromatin organization and gene activity in genomic imprinting. ***Curr. Opin. Genet. Dev***., 61, 17-24.

Prats-Puig A, Xargay-Torrent S, Carreras-Badosa G, Mas-Pares B, Bassols J, Petry CJ, Girardot M, De Zegher F, Ibanez L, Dunger DB, Feil R*, Lopez-Bermejo A* (2020). Parental influence on placental C19MC methylation: epigenetic programming of offspring's size. ***Int. J. Obesity,*** 44, 13-22.

Ghousein A., Feil, R.* (2020). Imprinted small RNAs unraveled: Maternal microRNAs antagonize a paternal-genome driven gene expression network. ***Molecular Cell*****,** 78, 3-5.

Llères, D, Moindrot, B, Pathak, R., Piras, V., Matelot, M., Pignard, B., Marchand, A., Poncelet, M., Perrin, A., Tellier, V., Feil, R.*, Noordermeer, D.*. (2019). CTCF modulates allele-specific sub-TAD structuration and imprinted gene activity at the *Dlk1-Dio3* and *Igf2-H19* domains. ***Genome Biol***., 20, 272.

Farhadova, S., Gomez-Velazquez, M, Feil, R.* (2019). Stability and lability of parental methylation imprints in development and disease. ***Genes*****,** 10, 12.

Tucci, V., Isles, A., Ferguson-Smith, A.C., 'Erice Imprinting Group' (including Robert Feil) (2019). Genomic imprinting and physiological processes in mammals. ***Cell***, 176, 952-965.

Sanli, I., Lalevée, S., Camissa, M., Perrin, A., Rage, F., Riccio, A., Llères, D., Bertrand, E., Feil, R.* (2018). Meg3 long non-coding RNA expression controls imprinting by preventing transcriptional upregulation *in cis*. ***Cell reports***, 23, 337-348.

Autres informations:

Etudiants actuellement en thèse ou en M2 dans l'équipe d'accueil.
Flavio DI MICHELE, PhD student. Début : Septembre 2021. Responsable : R. Feil. Ecole Doctorale : CBS2, Montpellier.
Cette année, nous avons uniquement des étudiants M1.

Etudiants ayant préparé ou soutenu leur thèse ou leur M2 dans l'équipe d'accueil au cours des six dernières années.
Dr. Sabina FARHADOVA, former PhD student. September 2018-November 2022. Responsable: R. Feil. Ecole Doctotale: CBS2, Montpellier. Acquired position : Postdoctoral Researcher, Madison, USA.

Dr. Claire DUPONT, former PhD student. September 2016-December 2020. Responsable: R. Feil. Ecole Doctotale: CBS2, Montpellier. Acquired position : Engineer on BIOCampus Microscopy Platform. (Claire did her Master-II with us, in 2016).

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Dr. Ildem SANLI, former PhD student. September 2012-December 2016. Responsable: R. Feil. Ecole Doctotale: CBS2, Montpellier. Acquired position : Postdoctoral Researcher, Institut Pasteur, Paris.

Cette proposition de stage s'adresse-t-elle spécifiquement à un étudiant scientifique, médecin ou vétérinaire ou bien est-il ouvert à tous les profils ?
En principe, oui, ce stage est ouvert à tous les profils.

Ce sujet peut-il donner lieu à une thèse ?
Oui.