TITLE

Functional consequences of missense mutations affecting a splicing factor in cancer.

LAB & PEOPLE

- Name of the hosting lab: UMR1078 Genetics, Functional Genomics and Biotechnology – Team Astre
  General activities of the lab: functional genomics
  Website: https://nouveau.univ-brest.fr/umr1078-genetique-genomique-biotechnologies/fr/page/astre-alternative-splicing-translation-regulation
  Number of staff / PhD: 51 (UMR1078), including 15 (team Astre)
- Supervisor name and contact:
  Dr Delphine Bernard - delphine.bernard@univ-brest.fr

TOPIC OF THE INTERSHIP

- Scientific context of the internship (max 20 lines)

Alterations in alternative splicing are common in cancer, and are often associated with the presence of somatic mutations in genes encoding components or regulators of the splicing machinery. Among these genes, *SF3B1 (splicing factor 3B subunit 1)* is the most frequently mutated in cancer, especially in hematological malignancies, including myelodysplasia. Research on SF3B1 is expanding internationally, as evidenced by the large number of articles published in the field. Nevertheless, the molecular physiopathologic mechanisms are still largely unknown. In particular, cancer-associated *SF3B1* mutations lead to a remodeling of the transcriptome, along with the production of novel alternative isoforms, the functional consequences of which remain to be explored. We hypothetize that not all cancer-associated SF3B1 variants are equivalent, some of which may be associated with a more aggressive disease phenotype. For this internship, we propose to compare the impact of different SF3B1 variants (all missense mutations) on the splicing of specific targets and on pathways of interest using dedicated assays in a unified cell model.

Keywords : functional genomics, missense variants, alternative splicing, cancer, cell lines.

Bibliography

Bergot T, Lippert E, Douet-Guilbert N, Corcos L and Bernard DG. Human cancer-associated SF3B1 mutations lead to a splicing modification of its own RNA. **Cancers** (Basel). 2020 Mar 11;12(3). pii: E652. doi: 10.3390/cancers12030652

Shiozawa, Y., et al., *Aberrant splicing and defective mRNA production induced by somatic spliceosome mutations in myelodysplasia.* Nat Commun, 2018. **9**(1): p. 3649.

Darman, R.B., et al., *Cancer-Associated SF3B1 Hotspot Mutations Induce Cryptic 3' Splice Site Selection through Use of a Different Branch Point.* Cell Rep, 2015. **13**(5): p. 1033-45.

- Tasks and duties entrusted to the student:

To conduct RNA extraction, quantitative RT-PCR and Western-Blots.
To culture and transfect suspension cells and adherent cells.
To analyse and report results.

- Skills to be acquired or developed: Cell culture, basic technics of molecular biology and biochemistry, possibly fluorescence microscopy.

PROFILE OF THE DESIRED STUDENT

- Minimum level of study required: Master in progress (internship for M2 students)

- Field(s) of study: molecular biology and genetics, functional genomics

- Scientific skills: molecular biology techniques, cell culture and basic biochemistry. Bioinformatics skills to analyse transcriptomic data would be appreciated.

- Language skills required: French or English (oral and written).

THE INTERNSHIP ASSIGNMENT:

Desired duration of the internship (in months): 5 months
Desired Starting date of the mission: flexible
Indicative weekly schedule: *35h / week*
Remuneration: *600€/month, paid on national SEA-EU funds for a maximum of 5 months; additional Erasmus grant could be asked to your own university.*
Internship agreement: *an internship agreement will be signed.*

To SEA-EU students:
If you're interested please send your CV and letter of motivation to the scientist in charge, delphine.bernard@univ-brest.fr.