PROJECT

Supervisor:	**Dr. Filippo Gagliardi, MD, PhD - Neurosurgeon**
Title:	**Methylation profiling on cerebral meningiomas: Epigenetic Analysis and Clinical Implications**
Curriculum:	***Neuroscience***
Link to the personal page of the University or relevant hospital site website:	**https://www.hsr.it/dottori/filippo-gagliardi**

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Meningiomas are the most common primary intracranial tumors. A significant subset exhibits aggressive growth and resistance to standard therapies. Prognostic stratification relies on histopathological criteria. However, this grading alone does not fully capture the biological heterogeneity of these tumors.

Genome-wide DNA methylation profiling has emerged as a robust tool for classification and prognostic prediction. Several studies have demonstrated that methylation-based subclasses identify clinically distinct groups (i.e., immunogenic [MG1], NF2 wild-type [MG2], hypermetabolic [MG3], and proliferative [MG4]) and outperform histological grading in predicting tumor recurrence.

The added value of the present project lies in applying and validating these molecular classifications in a clinically annotated surgical series with standardized neuroradiological review, histopathological reassessment according to WHO 2021 criteria, availability of matched blood samples, and prospective long-term follow-up. This design will allow us to test the clinical applicability of published methylation-based and multi-omic classifiers in a real-world neurosurgical cohort and to explore how molecular subgrouping may complement conventional prognostic variables in treatment decision-making.

Rationale and hypothesis

Despite growing evidence supporting methylation-based classification in meningiomas, its integration into routine clinical decision-making remains incomplete. This project will integrate DNA methylation profiling, CNV analysis, selected transcriptomic signatures, histopathological reassessment, and clinical-radiological data to refine risk stratification beyond WHO grading alone. The study is designed as a clinically focused validation and translational implementation project, applying established molecular frameworks to a well-characterized institutional cohort and creating a platform for future prospective expansion.

Objectives and specific aims

1. Perform DNA methylation profiling of surgically resected meningiomas.
2. Assign molecular subgroups using publicly available methylation-based classifiers.
3. Reassess histology of tumors operated before 2021 according to the WHO 2021 classification.
4. Compare recurrent tumors with corresponding primary specimens when available.

5. Evaluate the impact of genetic and epigenetic alterations on key biological pathways.
6. Correlate molecular subgroups with clinical-radiological features and survival after multimodal treatment.

Expected outcomes

This project will validate methylation-based classification in a clinically annotated institutional cohort by integrating histology, imaging, CNV profiles, selected transcriptomic signatures, treatment data, and follow-up. The expected impact is a translational workflow to improve recurrence-risk stratification, clarify histological–molecular discordance, and support personalized surveillance and adjuvant radiotherapy decisions.

Skills that the student should acquire (max. 600 characters including spaces):

Student will be required to develop skills focused on:

- Characterization of baseline neuroradiological features of meningiomas.
- Analysis of the epigenetic landscape of meningiomas using genome-wide DNA methylation profiling.
- Integration of epigenetic data with genomic and transcriptomic profiles to refine molecular classification.
- Evaluation of the efficacy of standard treatments (surgery and radiotherapy) across molecular and epigenetic subgroups.
- Correlation of molecular findings with clinical, radiological, and survival outcomes to improve prognostic stratification.

References (max. 15)

1. Ostrom, Q.T., et al., CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro Oncol, 2018. 20(suppl_4): p. iv1-iv86.
2. Wang, J.Z., et al., The multiomic landscape of meningiomas: a review and update. J Neurooncol, 2023. 161(2): p. 405-414.
3. Olar, A., et al., Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. Acta Neuropathol, 2017. 133(3): p. 431-444.
4. Sahm, F., et al., DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol, 2017. 18(5): p. 682-694.
5. Nassiri, F., et al., A clinically applicable integrative molecular classification of meningiomas. Nature, 2021. 597(7874): p. 119-125.
6. Bayley, J.C.T., et al., Multiple approaches converge on three biological subtypes of meningioma and extract new insights from published studies. Sci Adv, 2022. 8(5): p. eabm6247.
7. Choudhury, A., et al., Meningioma DNA methylation groups identify biological drivers and therapeutic vulnerabilities. Nat Genet, 2022. 54(5): p. 649-659.
8. Choudhury, A., et al., Hypermitotic meningiomas harbor DNA methylation subgroups with distinct biological and clinical features. Neuro Oncol, 2023. 25(3): p. 520-530.
9. Alexandrov, L.B., et al., Deciphering signatures of mutational processes operative in human cancer. Cell Rep, 2013. 3(1): p. 246-259.
10. Goldbrunner, R., et al., EANO guideline on the diagnosis and management of meningiomas. Neuro Oncol, 2021. 23(11): p. 1821-1834.
11. Wang, J.Z., et al., Molecular classification to refine surgical and radiotherapeutic decision-making in meningioma. Nat Med, 2024. 30: p. 3173-3183.
12. Chen, W.C., et al., Targeted gene expression profiling predicts meningioma outcomes and radiotherapy responses. Nat Med, 2023. 29: p. 3067-3076.

13. Landry, A.P., et al., A framework for using DNA methylation-based modelling for the clinical management of cranial meningioma. Neuro Oncol, 2026. 28: p. 430-439.
14. Maas, S.L.N., et al., Independent prognostic impact of DNA methylation class and chromosome 1p loss in WHO grade 2 and 3 meningioma undergoing adjuvant high-dose radiotherapy: comprehensive molecular analysis of EORTC 22042–26042. Acta Neuropathol, 2023. 146: p. 837-840.
15. Landry, A.P., et al., Validation and next-generation update of a DNA methylation–based recurrence predictor for meningioma: A multicenter prospective study. Neuro Oncol, 2025. 27: p. 1004-1016.