UroCCR
RÉSEAU FRANÇAIS DE RECHERCHE SUR LE CANCER DU REIN

Fiche de soumission de projet au Comité Scientifique et Ethique

PROJET TITLE: Epigenetic Clocks as Predictors of Distant Metastasis in Early-Stage Clear Cell Renal Cell Carcinoma : External Validation of the Juntendo University Study Using a Retrospective UroCCR Cohort

Acronym: JUNTENDO – UroCCR n°263

PROJECT LEAD:

X ACADEMIC ❒ INDUSTRIAL

Name / Organization: Juntendo University - Department of Urology
Adress: 2 Chome-1-1 Hongo, Bunkyo City, Tokyo 113-8421, Japan
Email : shorie@juntendo.ac.jp ; s-isotani@juntendo.ac.jp

PROJET TYPE :

❒ PROSPECTIVE **X** RETROSPECTIVE

X SINGLE-CENTER ❒ MULTICENTER

Partners (research teams) involved in the project:: ❒ OUI ❒ NON

If yes, please provide the following information for each partner:
Principal Investigator(s): Pr Jean-Christophe BERNHARD

Name / Organization: CHU de Bordeaux - Department of Urology
Adress: Pl. Amélie Raba Léon, 33000 Bordeaux
Email : jean-christophe.bernhard@chu-bordeaux.fr

PROJET DESCRIPTION

Background and rationale:
Although early-stage clear cell Renal Cell Carcinoma (ccRCC) generally shows favorable prognosis after surgery, a subset of small tumors develops distant metastasis. Current clinical predictors are insufficient to identify these high-risk patients. Preliminary data obtained by the team of Prof. Shigeo Horie at Juntendo University suggest that epigenetic clocks could provide a novel biomarker to guide postoperative management and adjuvant therapy decisions. In particular, they analyzed 30 cases of partial nephrectomy for ccRCC. During follow-up, 8 cases developed distant metastasis. They found that :
- Tumor size showed no significant association with mitotic burden.
- Mitotic burden showed a strong association with distant metastasis.
- Epigenetic mitotic clocks, especially epiTOC-type clocks (based on CpGs in PRC2 target regions), were strongly associated with postoperative metastasis.
- Higher epiTOC scores indicated greater risk of metastasis, suggesting these clocks may serve as effective biomarkers for biologically aggressive tumors beyond standard clinical features.
- HorvathS2018 and PCHorvathS2018 clocks were also effective predictors.

Aim:
To test the predictive value of epigenetic clocks in independent RCC cohorts through a multi-institutional external validation study.

Inclusion criteria:
1. Histological subtype: Clear cell RCC only.
2. Metastatic status: Ideally, 25 patients who developed distant metastases after surgery and 25 patients who remained metastasis-free.
3. Surgical procedure: Predominantly partial nephrectomy cases, with some radical nephrectomy cases included.
4. Histological grade: Preferably ISUP grade 1–2 cases.
5. Pathological stage: Preferably pT1 cases, if available.

Methods:
1. DNA Methylation Profiling: Analysis using Illumina EPIC arrays or equivalent.
2. Epigenetic Clock Calculation: epiTOC-type clocks, HorvathS2018, and PCHorvathS2018.
3. Outcome Assessment: Postoperative distant metastasis during follow-up.
4. Statistical Validation: Hazard ratios, Kaplan–Meier survival analysis, and C-index for discrimination.

Expected Impact:
- Establish whether epigenetic mitotic burden is a reproducible biomarker for metastasis in RCC.
- Provide a basis for clinical risk stratification and adjuvant therapy selection.
- Contribute to precision oncology in RCC by integrating molecular clocks with clinical features.

CLINICAL DATA / BIOLOGICAL RESOURCES:

- Which UroCCR data would you like to use for this project?
- Demographic data
- Diagnostic data
- Biological resource data
- Surgical data
- Histopathological data
- Follow-up data

- Will the project use data linked to the French National Health Data System (SNDS)?: ❒ YES **X** NO

- Does the project require biological resources? **X** YES ❒ NO

*** Type : frozen tissue samples (50 samples: 25 patients with distant metastases - 25 patients without distant metastases)**
*** Quantity : 50 mg or more**

- Does the project require medical imaging data?: ❒ YES **X** NO