Partner Search Form
Horizon Europe
Health

Date	12/06/2025	Deadline	

CONTACT

Organisation	INSERM-CEA-UGA U1292 Biosanté	**Department**	Health Department - Interdisciplinary Research Institute of Grenoble (IRIG)
Contact person	Nadia CHERRADI	**Email**	nadia.cherradi@cea.fr (PI) haiyet.chebli@cea.fr (EU contact)
City	GRENOBLE	**Website**	https://biosante-lab.fr/en/Pages/IMAC/Presentation.aspx
Country	FRANCE		

Organisation type

Research organisation type	☒ Research Organisation ☐ University ☐ Company ☐ Other	**Is your company a Small and Medium Sized Enterprise (SME*)?** **Number of employees: 3**	☐ YES ☒ NO

Your enterprise is an SME if:
- it is engaged in **economic activity**
- it has **less than 250 employees**
- it has either an **annual turnover not exceeding €50M**, **or an balance sheet total not exceeding €43M**
- it is **autonomous**

For the definition of SMEs, look at: http://ec.europa.eu/growth/smes/business-friendly-environment/sme-definition_en

Short introduction of key areas of institute's research:

Partner Search Form
Horizon Europe
Health

Former participation in an FP European project?	☒ YES ☐ NO
Project title / Acronym:	Validation in vivo of immune biological indicators of radiation exposure to use for emergency situations, the determination of health effects and molecular epidemiology"/ VIBRATO
Activities performed:	In the frame of the "Open Project for the European Radiation Research Area (OPERRA) Cell Biology: - In vitro: Effect of radiation on mRNA stability regulators (RNA-Binding Proteins) and on the target inflammatory genes of RNA-BP. - Ex vivo: Identification of novel biological indicators (inflammatory and stress-related genes) of cancer patient response to radiotherapy, in relation with radiation dose and time post-exposure (serum).

Expertise / Commitment offered

Description of your expertise:

Tumor and circulating microRNAs in adrenocortical cancer progression and aggressiveness - Diagnostic and therapeutic implications

Scientific context

Our research focuses on the role of microRNA deregulations in adrenocortical cancer progression and aggressiveness. Our approach is marked by a strong translational emphasis, bridging fundamental discoveries with clinical applications. Aberrant microRNA expression has been implicated in tumor progression, metastasis, and resistance to therapy, underscoring their significance as therapeutic targets and diagnostic/prognostic markers. In the last five years, we have dedicated our efforts to unraveling the intricacies of these processes, focusing on three primary objectives: **(1)** to elucidate the mechanisms underlying microRNA-mediated aggressiveness in adrenocortical cancer (ACC), **(2)** to develop microRNA-based anticancer therapies and **(3)** to discover high-performance biomarkers for ACC patient management and follow-up, aligning with the principles of precision medicine.

Highlights

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine cancer with very limited therapeutic options. We have previously shown that a massive deregulation of **microRNAs** is a hallmark of theses tumors (1-3). We identified two target genes of two overexpressed microRNAs that we found implicated in ACC invasiveness (3). Using Lipidots-mediated **nanovectorization of microRNA inhibitors in vivo**, we brought the proof of concept that

targeting these two oncogenic microRNAs in ACC impairs tumor growth and metastasis (4, 5). More recently, we discovered that the constitutive activation of **Wnt/β-Catenin signaling pathway** in ACC (1) is involved in the overexpression of many poor prognosis-associated microRNAs at the tumor tissue and cancer cell level (6, 7) and (2) **modulates extracellular vesicle (EVs) biogenesis/secretion and promotes oncogenic microRNA and protein loading into EVs** (Bangoura et al., in preparation). These findings underscore microRNA-mediated mechanisms as integral players in the oncogenic action of the Wnt/β-Catenin pathway in ACC. We developed a shared website called miRViz to help biologists to visualize their microRNA datasets using graph theory tools (8). In tight collaboration with the European ENSAT (https://ensat.wildapricot.org/) (9) and the National COMETE (https://www.sfendocrino.org/ comete-cancers-de-la-surrenale/) networks for the study of adrenal tumors, we have identified a potent **3 microRNA-circulating signature** which is predictive of recurrence risk for ACC (NCT02672020 COMETE TACTIC) (Denis et al., in preparation). Our findings highlight the importance of further exploring microRNA-based diagnostics and therapies in ACC and other cancers with dysregulated Wnt/β-Catenin signaling.

Projects

1- Deciphering the function of microRNAs in adrenocortical cancer at the single cell level

MicroRNAs are recognized as key players in a large number of carcinogenesis processes ranging from initiation, progression and metastasis formation. They raise many hopes as therapeutic treatment targets. However, the first drug candidate MRX34, which mimics a microRNA, proved to be a failure in patients because it was too toxic. It is therefore urgent to better understand the mode of action of microRNAs in order to design new therapeutic strategies. Indeed, the tumor microenvironment is complex and heterogeneous, meaning that microRNAs might act differently in distinct subpopulations of cells within the same tumor. Investigating microRNA-target interactions in individual cells will enable us to gain a deeper understanding of how microRNAs regulate gene expression in this context. Of note, although mRNA sequencing at the single-cell level has been a routine technique for the last ten years, microRNA sequencing and even more microRNA/mRNA co-sequencing in the same single cell are still in the development stage. We propose to use two cutting-edge technologies for this: **microRNA/mRNA co-sequencing experiments, at the single cell level**, and the prediction of microRNA expression with **artificial intelligence techniques** (AI, including neural networks and XGBoost). This program is supported by the CEA through a PhD fellowship (CFR 2024-2027) and will benefit from the contribution of two other projects, which end respectively in 2025 and 2026 (extendable): a thesis financed by "l'Ecole de l'Inserm-Pfizer Innovation", and a multi-team project financed by AVIESAN ITMO CANCER INSERM. We have already enabled rigorous statistical analysis of co-sequencing data at the single cell level, which will be used during the next

contract (10). A collaboration is planned with the Gipsa-Lab, Grenoble, an expert in machine learning/AI. We expect important findings related to the biology of the **modes of action of microRNAs from this state-of-the-art co-sequencing technic at the single-cell level**, and our expertise in the analysis of these data. The multidisciplinary expertise of the team (Biologists, bioinformaticians and clinicians), is key in order to exploit at best such experiments and data.

2- Impact of aberrant activation of Wnt/β-Catenin-signaling pathway in adrenocortical carcinoma on small extracellular vesicle-mediated metastasis and immune escape

The striking association between numerous deregulated microRNA and ACC patient prognosis suggests that they might have a key role in the physiopathology of these highly aggressive tumors, nearly half of which harbor constitutive activation of Wnt/β-Catenin signaling due to β- Catenin (CTNNB1) or ZNRF3 mutations. We found that **mutated β-Catenin orchestrates the overexpression of dozens of microRNAs in ACC**, a subpopulation of which is released into the extracellular compartment within **small extracellular vesicles (sEV)** (Bangoura et al, in preparation).
Cancer cell-derived small extracellular vesicles are now recognized as key players in cell-to-cell communication within the tumor microenvironment and at the systemic level. They carry a diverse cargo of proteins, nucleic acids (DNA, RNA), lipids, and metabolites. Tumor-derived sEV can transfer molecules that promote angiogenesis, pre-metastatic niche formation, and suppression of anti-tumor immune responses. sEV found in biological fluids such as urine or blood represent an excellent non-invasive source of biomolecules for molecular cancer profiling (proteins, non-coding RNAs such as microRNAs, etc.) with diagnostic and prognostic potential. Several oncogenic pathways, including the RAS/MAPK and PI3K/AKT pathways, are known to increase sEV production and alter their content and function. This enhanced production may facilitate intercellular communication and the spread of pro-tumorigenic signals. To date, the **functional impact of aberrant activation of the Wnt/β-Catenin signaling pathway on the biogenesis, composition, and function of small extracellular vesicles remains largely unknown**.
We have acquired expertise in the preparation and qualification of small extracellular vesicles in accordance with the **recommendations of the International Society for Extracellular Vesicles (MISEV 2023)** for their isolation, characterization, and functional analysis. We qualify sEV through nanoparticle tracking analysis (NTA) for size and concentration, expression of specific markers by western blot, electron microscopy, and atomic force microscopy. We aim at deciphering the impact of aberrant Wnt/β-Catenin signaling on EVs secretion, molecular content (microRNAs and proteins) and **function in the tumor microenvironment**. Two components of the tumor microenvironment will be considered to study the role of sEV in ACC progression: vascular endothelial cells and immune cells. This will be conducted using mastered methodologies in the team, namely 3D heterotypic

spheroids (cell-to-cell communication) and in vivo (tumor growth and metastasis).

3- Circulating microRNAs to advance cancer biomarker discovery and precision medicine

In addition to our fundamental research on microRNAs in ACC pathogenesis, we have taken advantage of the stability of microRNAs in biological fluids to develop expertise in the measurement of serum microRNA levels, in order to identify non-invasive biomarkers for the management of ACC patients. We could show that **patients with low levels of a single microRNA post-surgery have better survival** (NCT02672020, Oreglia et al, 2020). We further improved this signature by showing that the combination of **3 microRNAs** is even better at predicting survival (Denis et al, in preparation). We are currently involved in the COMETE-CARE clinical trial (NCT05754892, 2023-2029), which aims to validate this signature for potential transfer into clinical routine. In parallel, we aim to assess whether this signature is preserved in small extracellular vesicles and whether it offers greater diagnostic potential than that found in the whole serum from ACC patients.

References

1. Chabre O, Libe R, Assie G, Barreau O, Bertherat J, Bertagna X, Feige JJ, Cherradi N. Serum miR-483-5p and miR-195 are predictive of recurrence risk in adrenocortical cancer patients. Endocr Relat Cancer. 2013;20:579-94.
2. Cherradi N. microRNAs as Potential Biomarkers in Adrenocortical Cancer: Progress and Challenges. Front Endocrinol (Lausanne). 2015;6:195.
3. Agosta C, Laugier J, Guyon L, Denis J, Bertherat J, Libe R, Boisson B, Sturm N, Feige JJ, Chabre O, Cherradi N. MiR-483-5p and miR-139-5p promote aggressiveness by targeting N-myc downstream-regulated gene family members in adrenocortical cancer. Int J Cancer. 2018;143:944-57.
4. Reda El Sayed S, Cristante J, Guyon L, Denis J, Chabre O, Cherradi N. MicroRNA Therapeutics in Cancer: Current Advances and Challenges. Cancers (Basel). 2021;13.
5. Reda El Sayed S, Nougarede A, Denis J, Cristante J, Navarro F, Chabre O, Guyon L, Cherradi N. Lipid nanoparticle-based delivery of miR-139-5p and miR-483-5p inhibitors impairs growth and metastasis of adrenocortical carcinoma. Submitted.
6. Cristante J, Reda El Sayed S, Denis J, Ragazzon B, Hantel C, Chabre O, Guyon L, Cherradi N. Aberrant activation of Wnt/β-Catenin signaling pathway drives the expression of poor prognosis-associated microRNAs in adrenocortical cancer with a major impact on miR-139-5p and its host gene PDE2A. bioRxiv. 2023:2023.02.10.527992.
7. Justine Cristante, Soha Reda El Sayed, Josiane Denis, Walid Bertal, Catherine Pillet, Bruno Ragazzon, Constanze Hantel, Olivier Chabre, Laura Fancello, Laurent Guyon, Cherradi N. A β-Catenin–miR-139-5p/Phosphodiesterase 2A Axis Drives Tumor Progression in Adrenocortical

Partner Search Form
Horizon Europe
Health

Carcinoma and Reveals LEF1 as a Robust Activity and Prognostic Marker. Submitted. 2025.
8. Giroux P, Bhajun R, Segard S, Picquenot C, Charavay C, Desquilles L, Pinna G, Ginestier C, Denis J, Cherradi N, Guyon L. miRViz: a novel webserver application to visualize and interpret microRNA datasets. Nucleic Acids Res. 2020;48:W252-W61.
9. Oreglia M, Sbiera S, Fassnacht M, Guyon L, Denis J, Cristante J, Chabre O, Cherradi N. Early Postoperative Circulating miR-483-5p Is a Prognosis Marker for Adrenocortical Cancer. Cancers (Basel). 2020;12.
10. Velut L, Fancello L, Cherradi N, Guyon L. Single-cell microRNA-mRNA co-sequencing techniques convey large potential for understanding microRNA regulations but require careful and systemic approaches. Nat Commun. 2025;16:5255.

Keywords specifying your expertise:	Endocrine-Related Cancer - Adrenocortical Cancer - MicroRNA - RNA-binding proteins - Post-transcriptional regulation - transcriptome - miRnome - Extracellular vesicles - Cell signaling - Diagnostic and prognostic biomarkers - Bioinformatics
Commitment offered:	☒ Research ☐ Demonstration ☐ Training ☒ Technology ☐ Dissemination ☐ Other:

Interested in participation in project types:			
	☐ Research & Innovation Action	☐ Innovation Action	☐ EIC Pathfinder

Work Programme research areas: indicate your interest

Health

- Mode of action of microRNA
- MiRNA expression at the single cell level / Identification of miRNA target genes in cancer cells
- Diagnostic and Therapeutic applications of extracellular vesicle-carried miRNA
- miRNA as non-invasive circulating biomarkers

Call topic(s):

HORIZON-HLTH-2025-01-TOOL-02: Advancing cell secretome-based therapies

Do you have other partners for this topic (which partners/country)?	Yes, The French COMETE Network (experts and reference centers for the study of Adrenal tumors) Coordinated by Cochin Hospital, Paris, France

Partner Search Form
Horizon Europe
Health

HNN 3.0
HEALTH-NCP-NET

Profile of partner sought

Role	☐ technology development	☒ research	☐ training
	☐ dissemination	☐ demonstration	☐ other _____
Country /region	☐ Any Europe/North America/South America		
Expertise required	miRNA detection – miRNA in situ hybridization – analysis of miRNAs at the single cell level – extracellular vesicle isolation and characterization – cancer biology – tumor microenvironment		

I agree with the publication of my contact data: ☒ YES ☐ NO