# *GRANTS ON THYROID CANCER*

Thyroid cancer is the most frequent endocrine malignancy. The majority of cases are differentiated tumors, that are usually well cured with a good prognosis; however they occasionally progress to more aggressive variants associated with poor prognosis. These patients represent a clinical challenge, as no effective therapies are available yet.

**AIRC-IG2021-ID26107- PI Angela Greco_ SENESCENCE IN THYROID CANCER PROGRESSION AND THERAPY RESISTANCE: PRECLINICAL STUDIES AND THERAPEUTIC IMPLICATIONS**

Senescence has been historically described as a tumor-protecting mechanism; however, recent evidence indicates that their accumulation in cancer is detrimental. Senescent cells are involved in tumor resistance, recurrence and aggressiveness. The aim of this project is to define the role of senescence (also induced by therapy) in the progression, response and resistance to therapies of thyroid cancer. The possibility to target thyroid tumor cells by senolytic approaches (pharmacological elimination of senescent cells) will be explored. The results will help to unveil new possible therapeutic approaches for the most aggressive tumor forms that are still incurable

**Bandi Linee di Ricerca 2023 - Progetto Linea3 “”-D/22/01C – PI Mara Mazzoni_ DISSECTING THE ROLE OF INNERVATION IN THYROID CANCER**

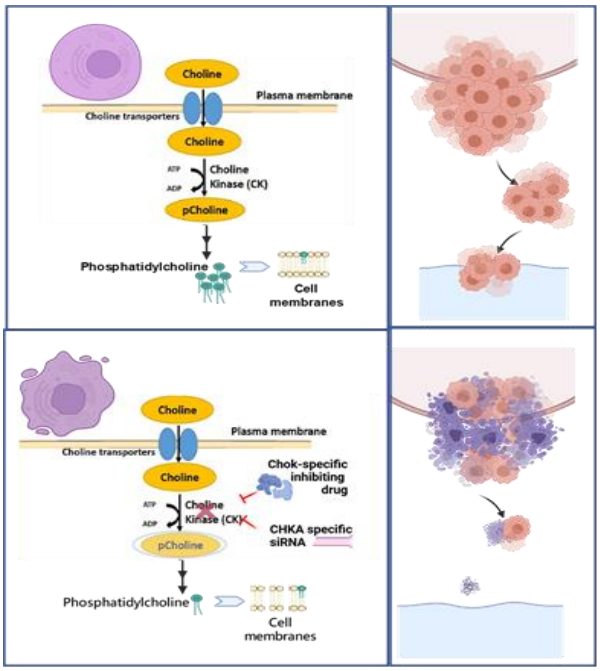
Nerves infiltrating tumors represent active components of the tumor microenvironment, playing an important role in cancer initiation and progression and providing potential targets for cancer treatment. Some works propose the involvement of innervation in the pathogenesis of thyroid cancer, even if its role remains to be established. The aim of this study is to explore, through in vitro and in silico approaches, the contribution of innervation in thyroid cancer progression, in order to produce preliminary data providing the basis and the rationale for planning future projects. The results will provide new knowledge about innervation as a mechanism contributing to thyroid tumor progression, helping to unveil new potential druggable targets for patients who do not respond to standard therapies.

## *GRANTS ON OVARIAN CANCER*

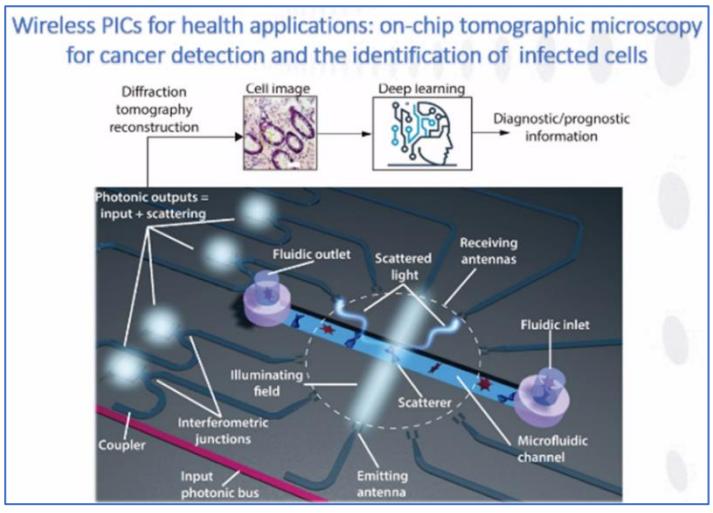
**AIRC IG-26066 PI Marina Bagnoli. "HARNESSING ALTERED CHOLINE METABOLISM TO HINDER CHEMORESISTANCE AND AGGRESSIVENESS OF OVARIAN CANCER".**

Epithelial ovarian cancer is a highly lethal disease difficult to diagnose and treat. We contributed in defining the *cholinic phenotype*, as a new ovarian cancer hallmark characterized by increased intracellular phosphocholine (PCho) content sustained by increased activity/expression of Choline kinase alpha (Chokα/CHKA).

We hypothesize that the *cholinic phenotype* fosters OC cells aggressiveness and survival by maintaining phospholipids' homeostasis, affecting anti-oxidant defense and membrane properties thus ultimately favoring peritoneal dissemination. Aim of this project is to assess Chokα druggability and the contribution of the cholinic phenotype in the pro-tumorigenic niche.

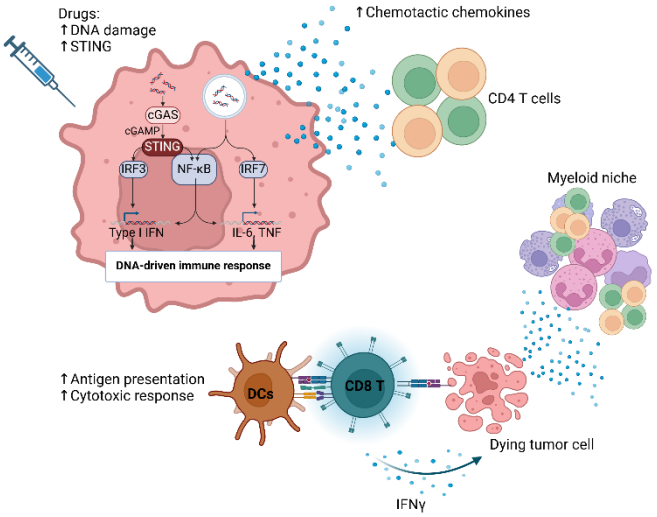



**HORIZON-EIC-2022-PATHFINDEROPEN-01- 101099663 DISRUPT (2023-2026) Project "On-chip tomographic microscopy: a paraDIgm Shift for RevolUtionizing lab-on-a-chiP bioimaging technology"** (PI: Universitat Politecnica de Valencia); Partner PI for INT: Delia Mezzanzanica




The project is part of the prestigious European Pathfinder program for the improvement of biomedical imaging and early diagnosis of various diseases including cancer. In particular, the DISRUPT project aims to revolutionize the field of biomedical imaging by developing an integrated microscope combining photonics and wireless tomography on a chip, with microfluidics and artificial intelligence for the early diagnosis of cancer and infectious diseases. Tomography is a biomedical imaging technique commonly used in conventional CT scans capable of creating detailed images of internal organs, tissues, bones, etc. In the DISRUPT project, tomography will be used on a photonic chip in which a microfluidic system will allow the cells to slide to obtain images from refractive index maps with artificial intelligence systems. The ultimate goal is to use the technology to distinguish tumor cells from benign cells for early diagnosis and/or response to therapy.

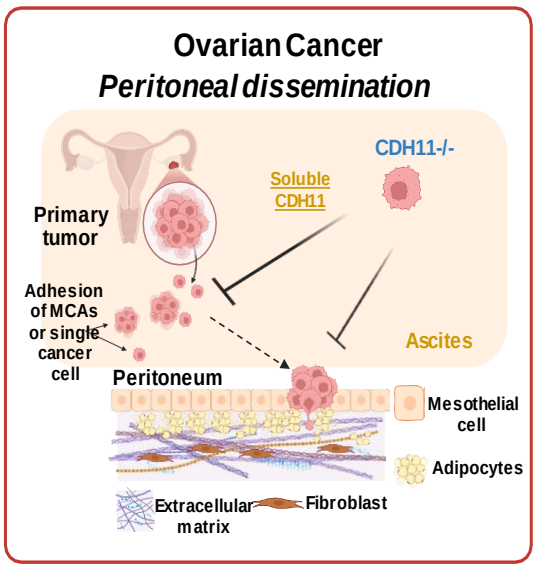
**PNRR-MAD-12375663: Overcoming PARPi resistance in ovarian cancer: from biology to clinical application** (PI Centro di Riferimento Oncologico di Aviano). Partner PI for INT: Delia Mezzanzanica




High-grade serous ovarian carcinoma is a relatively uncommon neoplasm but with a very high lethality. In recent years, the use of PARP inhibitors, in maintaining the first line of treatment, has significantly improved the prognosis of these patients. Unfortunately, over time, most of them develop disease recurrences that are resistant to treatment, leaving few valid therapeutic options. The aim of this project is to understand the causes of the development of resistance to treatment and consequently identify strategies to overcome these resistances and develop predictive biomarkers of response. Using a multidisciplinary approach and highly innovative technologies, we expect to provide useful elements for a better molecular characterization of patients in order to identify new and more effective therapies and offer increasingly personalized treatment modelled on the characteristics of each tumor.

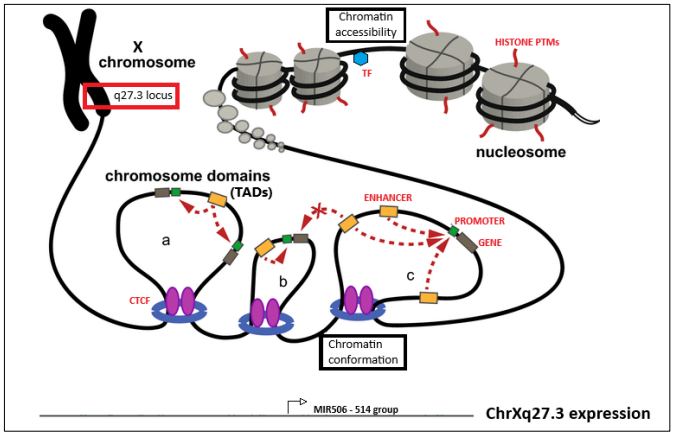
**BANDO RICERCA CORRENTE –**

**Linea 2 - PI Antonella Tomassetti. "CDH11 as new biomarker of metastases and master regulator of cancer cell plasticity in different metastatic routes"**




Epithelial-mesenchymal plasticity (EMP) emerges as a key regulator of metastatic outgrowth. This plasticity requires adhesion mechanisms which involve cell-cell- and cell-matrix-associated molecules for tumor cell growth and migration. High grade serous ovarian carcinoma (HGSOCs), the most frequent OC, only diffuses within the peritoneal cavity and is characterized by two different growing conditions, adherent vs suspension; the cell phenotypes of the two populations change in term of adhesion characteristics and intracellular signalling activation. Molecular and biological evidences indicate that the mesenchymal cadherin 11, CDH11, is a determinant of the EMP necessary for metastasis formation. Aim of this project is to assess in HGSOC CDH11 biological role during OC progression and to evaluate the potential of CDH11 of being a biomarker of aggressiveness.

**LINEA1- PI Andrea Rizzo. "ROLE OF CHROMATIN ORGANIZATION IN REGULATING ChrXq27.3 miRNAs' CLUSTER EXPRESSION TO REFINE ITS PROGNOSTIC IMPACT IN ASSESSING RISK OF RELAPSE"**




Despite advancements in treatment, the majority of Ovarian Cancer (OC) patients relapse after initial therapy, highlighting the critical need for accurate prognostic and predictive models to improve patient outcomes. OC patients who are classified as low risk for disease progression are those able to maintain the expression of the ChrXq27.3 miRNA's cluster. Understanding the mechanisms underlying the aberrant downregulation of this cluster is essential for improving prognostic accuracy and treatment strategies. To address this, we plan to use a combination of molecular biology and bioinformatics pipelines for analyse the epigenetic and epigenomic mechanisms responsible for the downregulation of ChrXq27.3 expression in OC, thereby enhancing its prognostic significance.

## *GRANTS on HEAD and NECK tumors and adult/pediatric brain tumors*

**AIRC IG23573 PI Loris De Cecco. "OPTIMIZING BIOMARKERS OF IMMUNOTHERAPY RESPONSE IN CLINICAL STUDIES SUMMARIZING HEAD AND NECK CANCER NATURAL HISTORY "**

Head and neck squamous cell carcinoma (HNSCC) accounts for 139,000 new cases yearly in Europe. The TNM classification (VIII edition, 2017) is the standard staging system. Early-stage diagnosis offers a high chance of cure, but about two-thirds of patients are diagnosed at advanced stages, with 27-50% relapsing within two years. Long-term survival rates remain low, and current treatments have reached their toxicity limits. Due to the common loco-regional recurrence pattern, achieving objective response and delaying disease progression are unmet clinical needs. Checkpoint inhibitors have revolutionized HNSCC treatment, receiving FDA approval for cisplatin-resistant R/M cases and are expected to move to first-line therapy. However, varying patient responses highlight the importance of considering each tumor's molecular and genetic profile for optimal treatment. This research will evaluate existing biomarkers using materials from prospective clinical trials. Over a 5-year plan, covering all stages of the disease from curative to R/M settings, the study aims to deliver a significant short-term impact on HNSCC management.

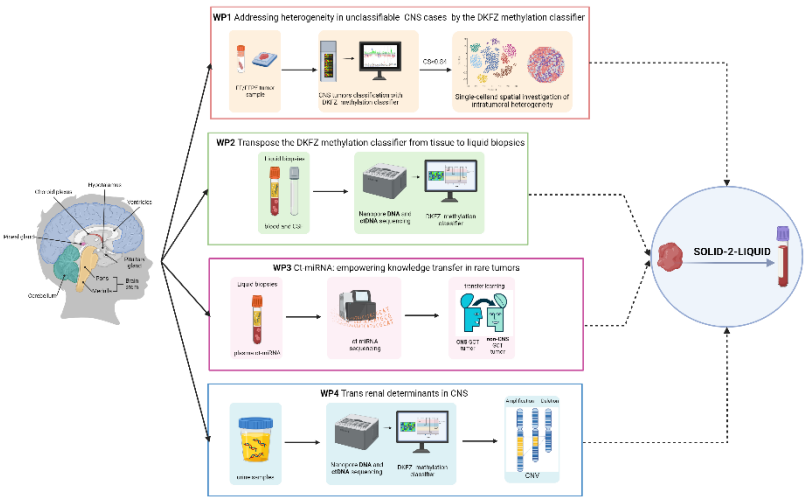
**PNRR BIOMATCH PNRR-MCNT1-2023-12377359 PI Loris De Cecco. "Matching primary tumor gene expression and blood analysis of HPV-negative squamous head and neck cancers (BIOMATCH - Head and Neck)".**


Our group at Fondazione IRCCS Istituto Nazionale Tumori previously developed and validated a molecular stratification in patients with curable head-and-neck squamous cell carcinomas (HNSCC) with prognostic and predictive values based on tumor tissue gene expression (GE). The present project aims at translating the subtype stratification on liquid biopsies exploiting a cohort of patients with curable HPV-negative HNSCC to forecast and easily monitor the risk of relapse after treatment. 300 newly-diagnosed patients with matched primary tumor pathological slides and longitudinal blood series will be collected prospectively for biological analyses including: i) multi-omics integration at bulk, single-cell, spatial levels for subtype stratification; ii) profiling of circulating biomarkers; iii) AI model development to implement longitudinal monitoring on liquid biopsies; iv) model development on tissue tumor slides to optimize classification for future applications in the clinical practice.

**NET-2019-12371188 PI Loris De Cecco. All-Ages Malignant Glioma: Holistic Management In The Personalised Minimally-Invasive Medicine Era - From Lab To Rehab - GLI-HOPE**

Diffuse Intrinsic Pontine Gliomas (DIPGs) progress rapidly with severe neurological symptoms and poor prognosis, with a median survival of up to 11 months. Standard treatment with radiotherapy provides temporary relief but does not stop tumor progression. DIPGs are linked to K27M mutations in the histone H3 gene (H3F3A or HIST1H3B), diffuse growth, and midline location. Including these tumors in DIPG treatment protocols may enhance understanding and outcomes. No prognostic biomarkers are currently used, but molecular and genetic analyses of biopsy samples have provided new insights. Non-invasive methods like real-time PCR and next-generation sequencing (NGS) are being explored to stratify patients and monitor tumor profiles. Plasma circulating miRNAs are emerging as potential disease markers. The gut-brain axis suggests intestinal microbiota may influence DIPG growth through immune modulation, and specific microbial signatures could be linked to prognosis. Radiomics offers additional diagnostic potential. This research seeks to combine molecular, genetic, microbiota, and imaging data using machine learning to improve personalized DIPG diagnosis, prognosis, and treatment.

**Associazione Bianca Garavaglia PI Loris De Cecco. "Shifting Pediatric Brain Tumor Diagnostics from Solid Tissue to Liquid-biopsies Approaches SOLID-2-LIQUID".**




Tissue specimens are the gold standard for analyzing tumor biology but require invasive procedures and provide only a single snapshot of the tumor. Liquid biopsies, using blood, CSF, or urine, offer a non-invasive alternative to determine genomic profiles, monitor treatment response, and assess drug resistance. Researchers at DKFZ developed a Methylation Classifier for CNS tumors using DNA methylation on tissue samples, enhancing prognosis and treatment strategies. This approach could be adapted for liquid biopsies, allowing biological insights to be transferred from tissue to blood, CSF, or urine. This study aims to: i) Use ctDNA in plasma for tumor characterization through methylation classifiers and genomic alterations. ii) Investigate ctDNA/ctmiRNA for disease monitoring and assess urine as a potential source of biomarkers in CNS tumors.

**BANDO RICERCA CORRENTE**

**Linea 3 Co-PI Armando Licata "The ecology of HPV-related cancers: bridging biology between head and neck cancer and cervical cancer to discover mechanisms of response in primarily chemo or chemoradiotherapy treated tumors".**

Human papillomavirus (HPV) 16 is a key carcinogen linked to about 5% of all cancers worldwide, particularly cervical cancer and oropharyngeal carcinoma (OPC). High-risk HPV types 16 and 18 drive cancer progression through viral oncoproteins E6 and E7, which disrupt cellular processes. This

project seeks to improve treatments for HPV-related OPC and cervical carcinoma (CC) by exploring their molecular heterogeneity and developing personalized therapies. Initial studies identified three gene expression clusters in CC with different prognoses and immune profiles, suggesting new targets for therapy. The study will use RNA sequencing, HPV integration pattern analysis, and gene signatures to predict chemo and radio-sensitivity. AI models will integrate clinical, molecular, microbiome, and treatment data to predict patient outcomes. Supported by extensive samples and collaborations, the project aims to enhance understanding of HPV-related cancers and optimize personalized treatments.

## *GRANTS on MICROBIOME*

**BANDI RICERCA CORRENTE**

**Linea 3 PI Debora Lenoci. "EVALUATING THE ROLE OF INTRATUMOR MICROBIOMA AND DIET EXOGENOUS MIRNAS IN THE PATHOGENESIS AND OUTCOME OF ENDEMIC AND NON ENDEMIC EBV-RELATED NPC (MICROBE-NPC)"**

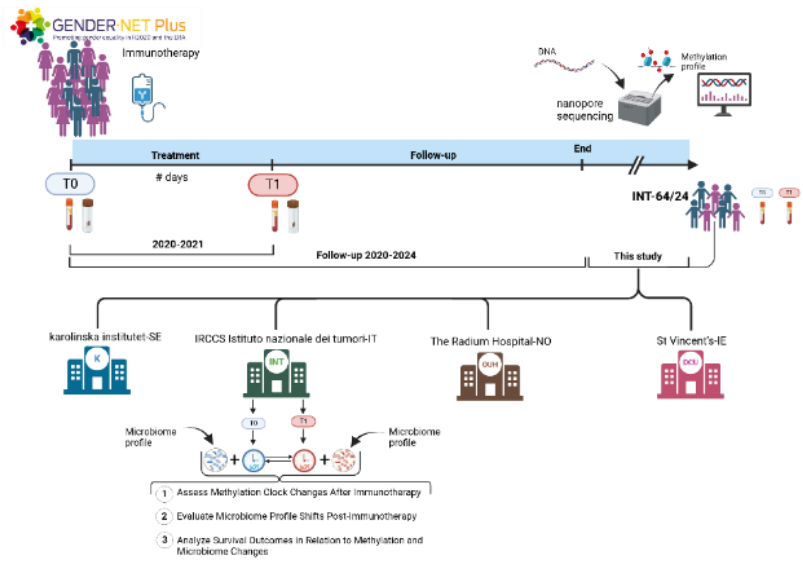
Epstein-Barr virus (EBV)-related nasopharyngeal carcinoma (NPC) is common in East and Southeast Asia but rare in Europe, where survival rates are lower. Differences may be due to EBV factors, population susceptibility, and environmental influences. Current research is based on Asian data. An international study of 1100 European NPC cases found no genomic differences between Asian and European patients, suggesting environmental factors like microbiota and miRNAs may influence NPC biology. Further research will explore these environmental impacts on NPC progression and treatment resistance. This study examines nasopharyngeal carcinoma (NPC) using the following cohorts: 112 NEA-NPC patients already profiled for gene and miRNA expression, 23 plasma samples from NEA patients, 25 Chinese NPC patients living in Italy, and gene expression data from EA-NPC in public repositories The aims are i) to assess microbiota and dietary impacts in a changed environment. Ii) to Analyze intratumoral microbiota differences across populations to identify ecological niches in EA and NEA NPC. Iii) to investigate food-derived circulating miRNAs in plasma and tumor tissue to understand their role in NPC biology and potential impact on treatment outcomes.

**Linea 3 coPI Chiara Dossena. AN INTEGRATIVE METAGENOMICS AND EPIGENOMICS APPROACH TO DISCLOSE THE BIOLOGICAL UNDERPINNINGS IN PEDIATRIC BRAIN TUMORS THROUGH NON INVASIVE METHODS.**

Malignant brain tumors are the most common solid cancers in children, showing diverse origins, genomic profiles, treatments, and outcomes. Advances in surgery, neuro-oncology, neuroradiology, and radiation have improved survival rates for some tumors, like low-grade gliomas and medulloblastomas. However, high-grade gliomas (HGGs) and recurrent pediatric brain tumors have poor outcomes, with current treatments offering limited life extension. This project introduces an innovative approach for HGGs by: i) Integrating diverse datasets to create comprehensive predictive and prognostic models ii9 Informing treatment decisions to potentially improve survival and quality

of life .iii) Enhancing model accuracy and reproducibility by combining multi-omics and clinical data, reducing biases and uncertainty .The project will utilize non-invasive procedures to develop robust prognostic models, optimize decision rules, and investigate biological features linked to outcomes. By incorporating decision theory, this research aims to improve clinical decision-making and guide treatment strategies, supporting better integration into healthcare systems.

**LINEA 4 PI Licata- coPI Dossena. "INTERCONNECTIONS BETWEEN AGING, EPIGENETICS, AND GUT MICROBIOTA: IMPLICATIONS FOR CANCER THERAPY AND OUTCOME PREDICTION (AEGIS)".**




Systemic cancer therapies, particularly immune checkpoint inhibitors (ICI), hold great promise but may inadvertently accelerate biological aging. Epigenetic clocks based on DNA methylation provide a sensitive measure for detecting changes in biological age, while the gut microbiome and proteomic profiles can offer additional insights into the biological impacts of these treatments. This study employs nanopore sequencing to generate high-resolution methylation data from both adult and pediatric cancer cohorts before and after ICI or chemotherapy. We will integrate this epigenetic data with microbiome and proteomic analyses, exploring how these multi-omics signatures correlate with treatment outcomes, toxicity, and potential age acceleration. Initial findings from breast cancer patients reveal significant, patient-specific methylation shifts post-ICI, indicating diverse epigenetic reprogramming. These observations suggest a multifaceted interaction between therapy, aging processes, and disease course. By refining and applying epigenetic clocks, we aim to detect and quantify accelerated aging in real time. Coupling these measurements with proteomic and gut microbiome data will illuminate mechanisms driving therapy-related aging and toxicity. Ultimately, the project aspires to guide clinicians in balancing treatment efficacy against long-term health impacts, helping preserve both lifespan and health span for cancer patients in an era of rapidly evolving ICI-based therapies.