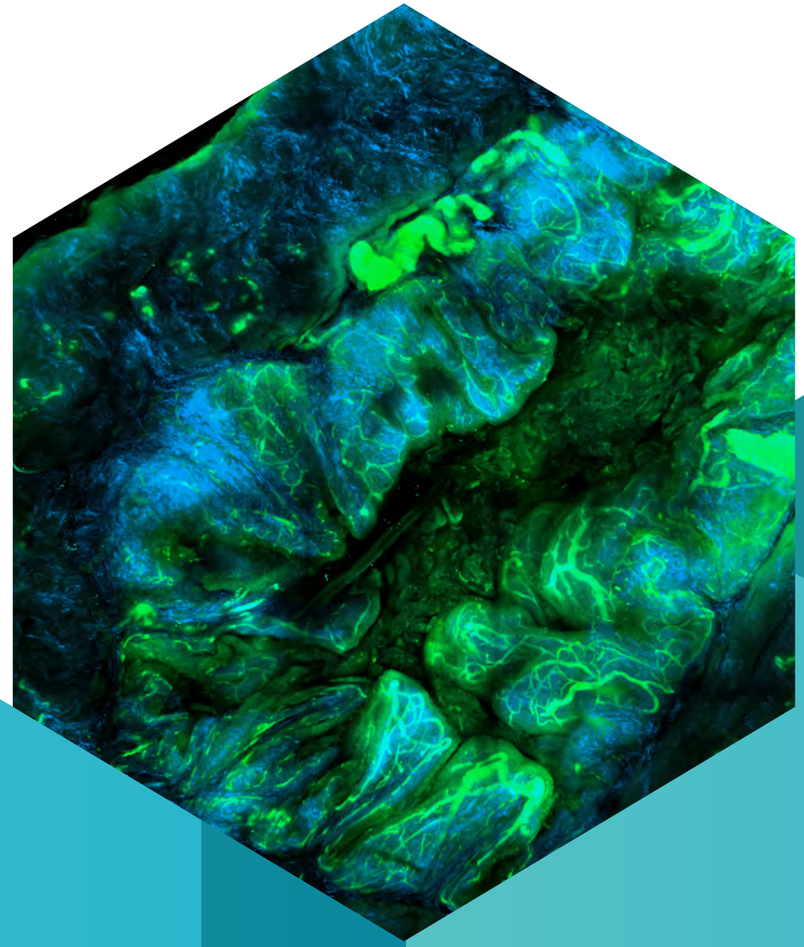
# CERIC

# for Cancer Research

Central European
Research Infrastructure
Consortium



ceric-eric.eu

# What is CERIC?

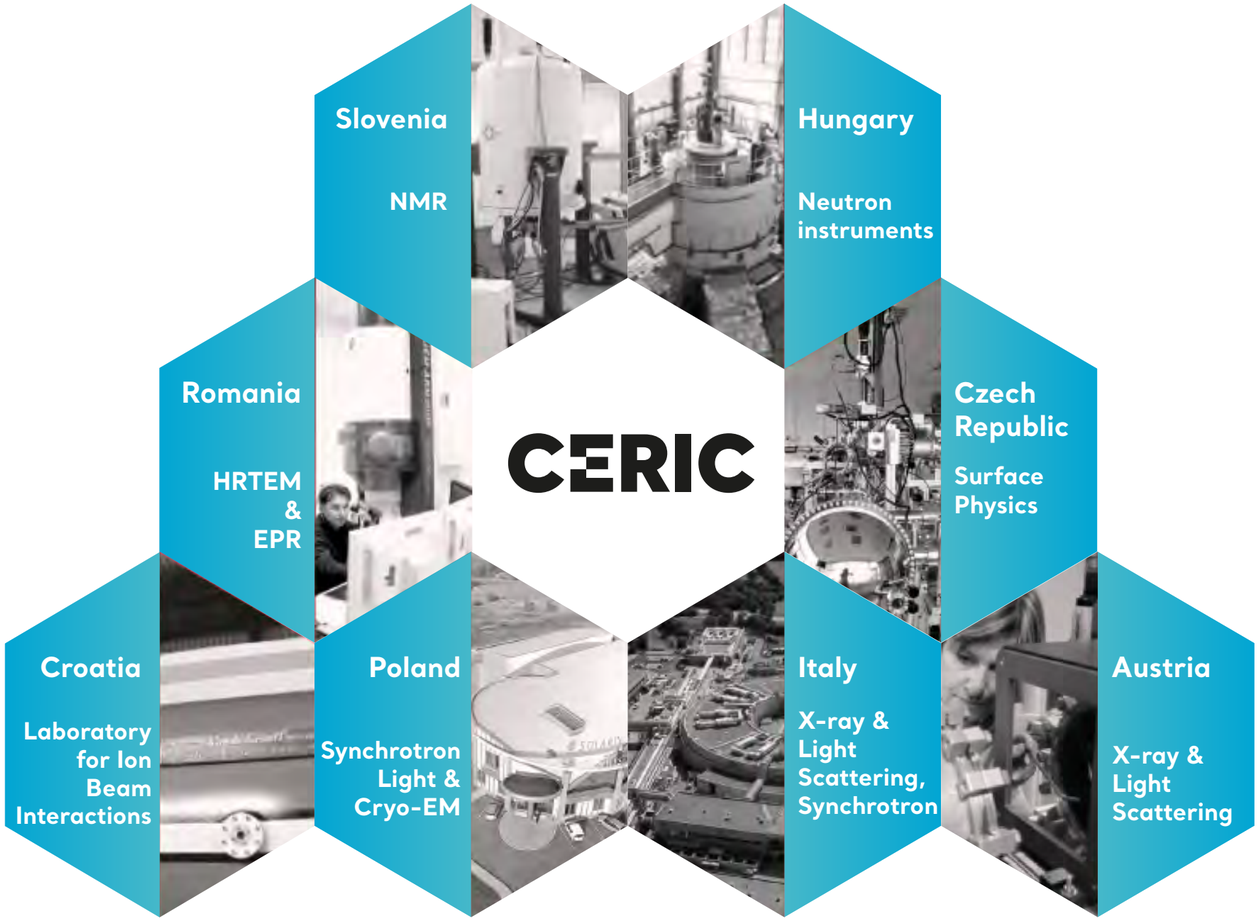
CERIC (Central European Research Infrastructure Consortium) is an integrated multidisciplinary research infrastructure for basic and applied research in the fields of materials, biomaterials and nanotechnology. It integrates leading national research institutes into a unique international infrastructure, having its statutory seat in Trieste- Italy, and its nodes distributed in Austria, Croatia, Czech Republic, Hungary, Italy, Romania, and Slovenia.

In each country, a Partner Facility (PF) ensures access and outreach to all national scientific communities and to users from all over the world, who compete for free access to more than 50 techniques available through a single entry point and based on the use of electrons, ions, neutrons and photons for the analysis and synthesis of materials.

A common support system allows the distributed staff to operate in an integrated way for transnational and cooperative projects and joint ventures. Each Member Country contributes to CERIC by making available and supporting a high-quality PF, which is continuously improved by being exposed to international users competing for access through peer-reviewed evaluation and selection of their proposals, based on excellence.

The PFs are strongly complementary to each other and act as a whole as an international agency providing support to the best researchers and research projects, contributing access to advanced analytical and synthesis facilities.

CERIC's international, pan-European approach, in line with the ERIC Regulation EC No 723/2009, avoids duplication and fragmentation in the research system, and increases integration and competitiveness of the European Research Area (ERA), speeding up East-West alignment in the ERA.



# Cancer research at CERIC

Fundamental and applied cancer research are among CERIC users' most investigated research topics. Their efforts span from cancer diagnostics to therapeutics, from studying critical DNA structures to drug delivery technologies. The following slides include some of the most recent and relevant research works related to cancer. Each slide contains a brief explanation of how each technique can help cancer research and a short description of the research work.

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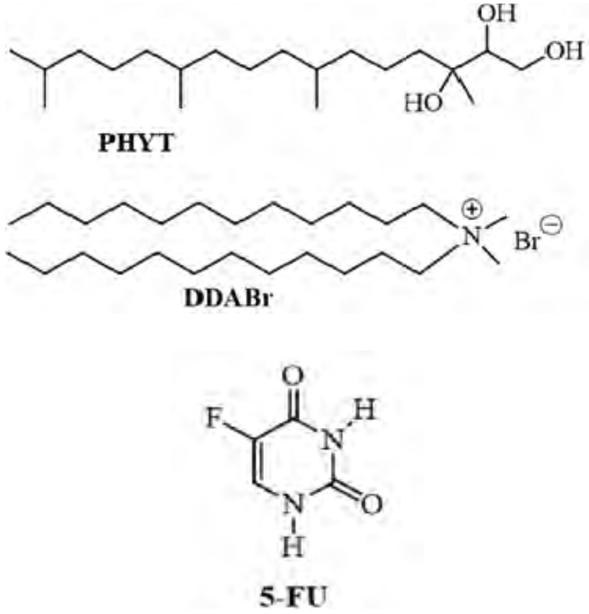
# FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

From tissues to complex cellular systems, the SISSI-Bio beamline offers an instrument that can provide information contributing to the tumour classification in terms of aggressivity and helps identify the action mechanisms of new drugs.

## Reference


Astolfi P., Giorgini E., Adamo F. C., Vita F., Logrippo S., Francescangeli O., & Pisani M., **Effects of a cationic surfactant incorporation in phytantriol bulk cubic phases and dispersions loaded with the anticancer drug 5-fluorouracil**. *Journal of Molecular Liquids* (2019).


*Chemical structures of phytantriol (PHYT), didodecyldimethylammonium bromide (DDABr), and 5-Fluorouracil*

## Increasing the payload of drug delivery carriers against cancer

**Phytantriol (PHYT)**, a cosmetic and food addictive, is characterised by attractive properties for biomedical applications since it's non-toxic, chemically stable, and biocompatible.

An example is given by the drug delivery of chemotherapy agents, such as **5-fluorouracil (5-FU)**. Experiments realised with the contribution of CERIC-ERIC revealed that the use of ionic surfactants (DDABr) influences the structure of Phytantriol, allowing for **increased drug loading**. The loading of 5-FU was verified by **Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR)** measurements at the SISSI beamline at the Italian CERIC partner facility at Elettra Sincrotrone Trieste.

This result opens for improvements in cancer treatments and reduced side effects by chemotherapy agents.

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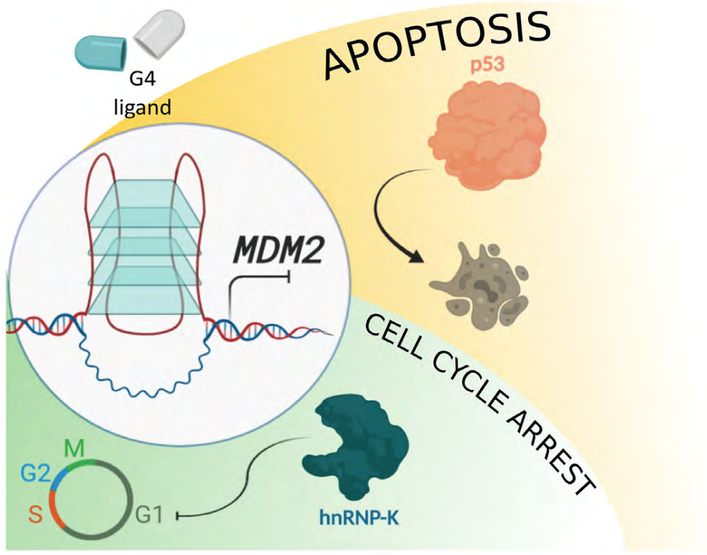
# NUCLEAR MAGNETIC RESONANCE (NMR)

NMR spectroscopy has demonstrated its potential in cancer research as a valuable tool for both cancer diagnosis and therapy. NMR-based experiments include metabolomics and molecular structure determination for diagnosis and cancer treatment.

## Reference


Lago S., Nadai M., Ruggiero E., Tassinari M., Marušič M., Tosoni B., Frasson I., Cernilogar F. M., Pirota V., Doria F., Plavec J., Schotta G., & Richter S. N. **The MDM2 inducible promoter folds into four-tetrad antiparallel G-quadruplexes targetable to fight malignant liposarcoma**. *Nucleic acids research* (2021)


*Graphical abstract of the research work (from the paper)*

## Rescuing p53 functionality for treating well-differentiated liposarcoma

**Well-differentiated liposarcoma** is a malignant neoplasia hard to diagnose and treat. Its primary molecular signature is the amplification of a genomic region containing the ***MDM2* gene**, which is the **master regulator of p53**, a tumour suppressor protein also called the Guardian of the Genome. In this tumour, the overexpression of *MDM2* enhances the **degradation of p53**, inhibiting its response.

A team of scientists exploited the presence of guanine-rich regions in the *MDM2* promoter capable of folding into G-quadruplexes (G4), a complex genomic structure at the centre of many CERIC-related works. In the present case, **Nuclear Magnetic Resonance (NMR)**, available at the Slovenian CERIC Partner Facility at the National Institute of Chemistry in Ljubljana, gave essential structural information about the G4s present in the promoter region of *MDM2*.

Scientists then targeted these regions with molecules capable of inducing the general suppression of *MDM2* by bonding with the G4 present in the promoter, thus **restoring the function of p53**. This work paves the way for the design of highly selective G4 ligands and, therefore, a possible cure for the well-differentiated liposarcoma.

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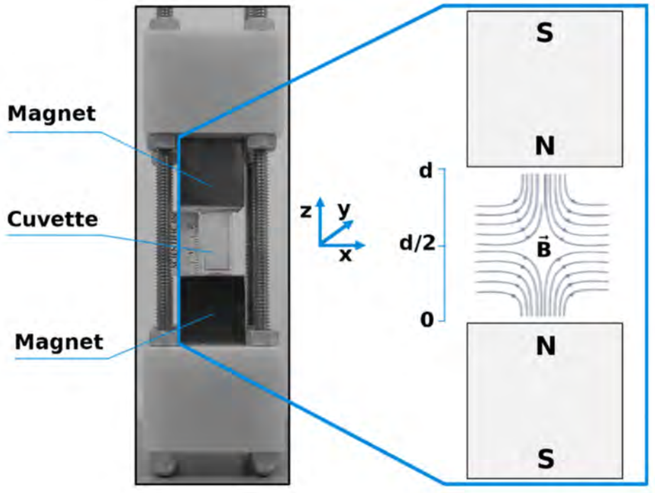
# SMALL ANGLE X-RAY SCATTERING (SAXS)

Small-angle X-ray scattering is a structure determining tool that operates in the range of 1 to 100 nm. This technique is employed to investigate anticancer drug activity to specific target molecules, screen tissues for melanoma and breast cancer detection, and examine the formulation of delivery systems for anti-cancer drugs.

## Reference


Digiacomo L., Quagliarini E., La Vaccara V., Coppola A., Coppola R., Caputo D., Amenitsch H., Sartori B., Caracciolo G. & Pozzi, D., **Detection of Pancreatic Ductal Adenocarcinoma by Ex Vivo Magnetic Levitation of Plasma Protein-Coated Nanoparticles**. *Cancers* (2021).


*Photograph and scheme of the MagLev platform (from the paper)*

## Magnetic levitation and nanoparticles for early diagnosis of pancreatic cancer

**Pancreatic Ductal Adeno Carcinoma (PDAC)** is a highly lethal disease, and is often asymptomatic in its first stages. Therefore, its diagnosis is frequently confirmed when distant metastases are already in place. Despite the scientific community's efforts, achieving an effective **early diagnosis** is still a big challenge.

A proof-of-concept study with the contribution of CERIC-ERIC employed **magnetic levitation** on **nanoparticles** to diagnose PDAC. Once exposed to the patients' body fluids, nanoparticles get coated from a plasma-derived protein layer. The composition of the coating, called **protein corona**, is personalised and connected to the **patients' health status**. Moreover, it can influence how nanoparticles float once exposed to a magnetic field.

**Small-Angle X-ray Scattering (SAXS)**, available at the Austrian CERIC Partner Facility at the Elettra synchrotron in Trieste, was employed to characterise the interaction among nanoparticles and human plasma. The results are **stimulating** and **encouraging** towards the research of an effective method for the early diagnosis of PDAC.

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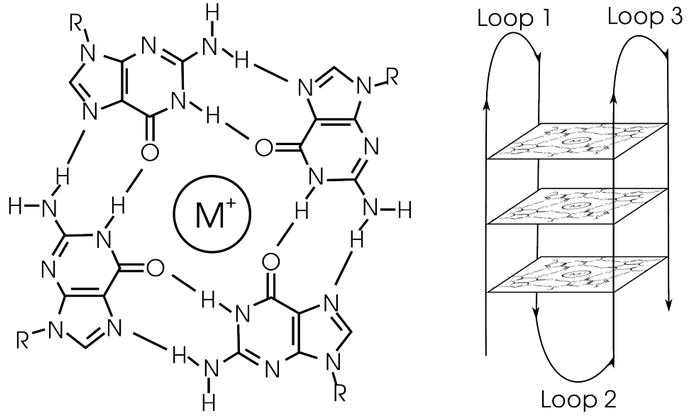
# ULTRAVIOLET RESONANT RAMAN (UVRR)

At IUVS beamline, the UV radiation produced by the synchrotron is used for Raman spectroscopy. This technique allows obtaining a structural fingerprint by which molecules can be identified. Examples include the investigation of antitumour drugs and the study of biological and biochemical processes of interest for cancer research.

## Reference


Di Fonzo S., Amato J., D'Aria F., Caterino M., D'Amico F., Gessini A., Brady J.W., Cesaro A., Pagano B. & Giancola C. **Ligand binding to G-quadruplex DNA: New insights from ultraviolet resonance Raman spectroscopy.** *Physical Chemistry Chemical Physics* (2020).


*Example of a G-quadruplex*
*(Author: Julian Huppert, Wikimedia Commons, CC BY-SA)*

## Raman spectroscopy for the investigation of new anticancer drugs

DNA and RNA can fold into a variety of alternative conformations. Recently, increasing attention has been focused on **G-quadruplexes**, a non-canonical structure identified in several regulatory regions of the human genome. This structure can control gene expression and be exploited for novel **anticancer treatments**.

Several techniques are currently employed to investigate the interaction among selected G4s and specific molecules. Research experiments, realised with the contribution of CERIC-ERIC, demonstrated that **Ultraviolet Resonant Raman (UVRR)** provides a straightforward method to study this interaction. The investigations were performed at the IUVS beamline at the Italian CERIC Partner Facility at Elettra Sincrotrone Trieste.

Ultraviolet Resonant Raman spectroscopy can be a powerful method for **investigating and developing** selective and potent G4-binding **molecules with anticancer activity**.

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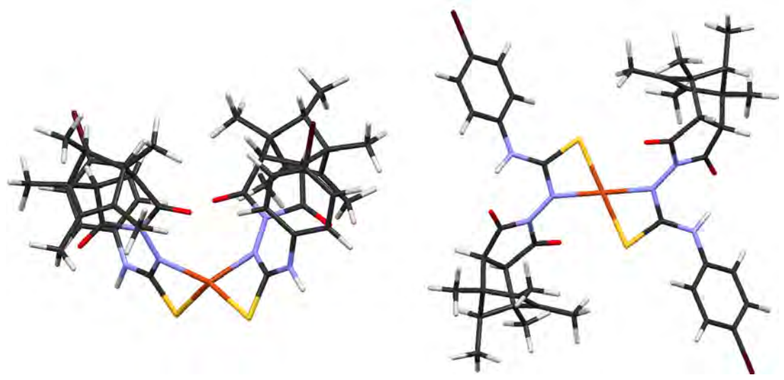
# X-RAY ABSORPTION SPECTROSCOPY (XAS)

XAS can probe the local structure around a selected atom regardless of the state of matter, providing structural information in a range of 3–5 Å around the metal centre. It has been applied in cancer studies to gain insights into the relationship between the structure and activity of anticancer drugs, such as copper complexes.

## Reference

Drzewiecka-Antonik A., Rejmak P., Klepka M., Wolska A., Chrzanowska A., & Struga, M., **Structure and anticancer activity of Cu (II) complexes with (bromophenyl) thiourea moiety attached to the polycyclic imide.** *Journal of Inorganic Biochemistry* (2020).



*Structural model of one of the copper-based compounds employed in the study*

## Copper-based anticancer drugs for the treatment of colon and prostate cancer

As a critical component of enzymes and proteins, **copper** plays a vital role in many biological processes. For instance, it is essential for **angiogenesis**, the formation of new blood vessels, a critical process for tumour growth and metastasis. However, it can also be a component of **anticancer drugs**.

A panel of nine different copper complexes was tested against several tumour-derived cell lines in comparison to well-known anticancer drugs, cisplatin and doxorubicin. **X-ray absorption spectroscopy**, available at the XAFS beamline at the Italian CERIC partner facility at Elettra Sincrotrone Trieste, was employed to gather **structural and chemical information** about the copper complexes.

Results suggest that specific copper-based compounds are promising for developing new effective drugs, especially for **colon and prostate cancer treatment**.

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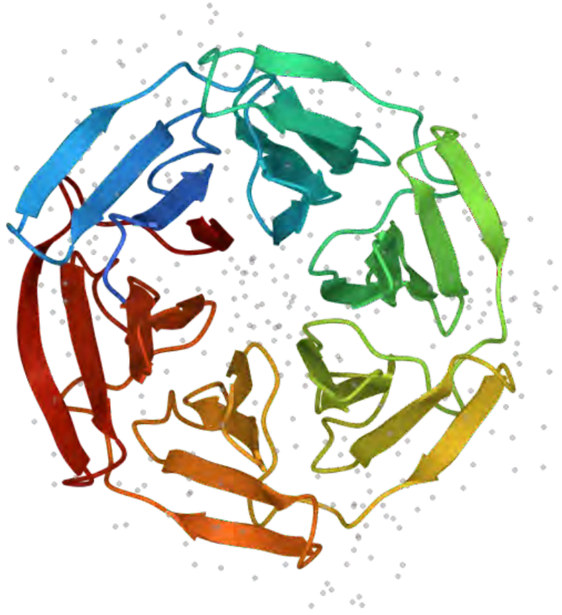
# X-RAY DIFFRACTION (XRD)

XRD1 can provide the three-dimensional structure of small and large molecules. Among its applications, there's the study of the structure and function of many biological molecules, including vitamins, drugs, proteins, and nucleic acids such as DNA.

## Reference


Matić S., Kekez I., Tomin M., Bogár F., Šupljika F., Kazazić S., Hanić M., Jha S., Brkić H., Bourgeois B., Madl T., Gruber K., Macheroux P., Matković-Čalogović D., Matovina M. & Tomić S., **Binding of dipeptidyl peptidase III to the oxidative stress cell sensor Kelch-like ECH-associated protein 1 is a two-step process**. *Journal of Biomolecular Structure and Dynamics* (2020).

*3D model of the KEAP1 protein*

## Understanding protein interactions to develop new cancer treatments

The **NRF2-KEAP1 pathway** is one of the primary regulators of oxidative **stress response in the cell**. The protein NRF2 is bound to KEAP1 in the cytoplasm in normal conditions. In contrast, in the presence of oxidative stress, DPP III competitively binds to KEAP1, displacing NRF2, which translocates into the nucleus mediating the expression of genes with anti-oxidative and protective functions. **Misregulations in this pathway are associated with resistance to chemotherapic drugs**. A better understanding of protein interactions within this pathway would give sensitive information for cancer research.

**X-ray diffraction (XRD)** studies, realised with the contribution of CERIC-ERIC, allowed to gain meaningful **structural details about the proteins involved and their interaction**. XRD experiments were performed at the XRD1 beamline at the Italian CERIC Partner Facility, Elettra Sincrotrone Trieste.

The knowledge acquired with this study advanced cancer research, giving new insights and better details, allowing for the **development novel cancer treatments**.

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# X-RAY FLUORESCENCE MICROSCOPY (XRFM)

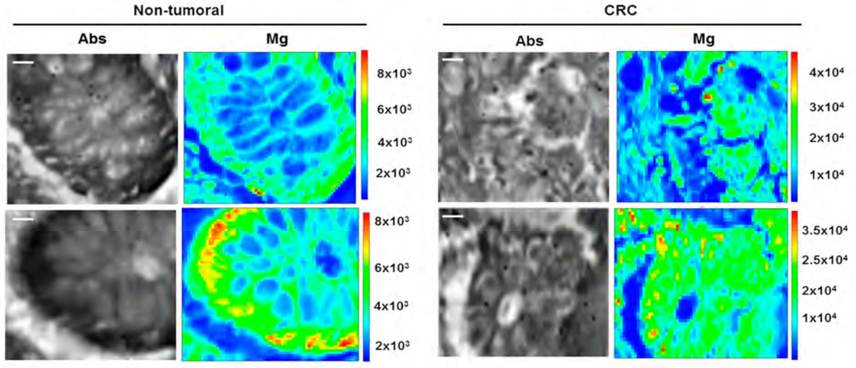
TwinMic beamline has been attracting the attention of the Life Sciences community thanks to its imaging and spectroscopic capabilities of interest in different types of cancer research. Examples include mapping the distribution of magnesium in various types of tumours to better understand its role.

## Mapping magnesium distribution in cancer for improved diagnoses

**Colorectal cancer (CRC)** represents the third most common malignant neoplasm accounting for approximately 1.8 million new cases per year. **Magnesium has been proposed to play a relevant role**. However, deeper analyses are needed to clarify the impact of the levels and distribution of magnesium in cancer.

In a proof-of-concept work, **X-Ray Fluorescence Microscopy (XRFM)** was employed to assess the morphology and the magnesium content distribution in healthy and tumour-derived tissues. The XRFM technique is available at the TwinMic beamline at the Italian CERIC Partner Facility at Elettra Sincrotrone Trieste.

The results provided evidence of a **direct correlation** between the total **content and distribution of magnesium** in tissues and **colorectal cancer**. This observation highlights the importance of developing a more comprehensive analysis of magnesium levels in colorectal cancer to improve diagnostic methods.




*XRFM analysis of healthy (left) and colorectal cancer tissue (right) (from the paper)*

## Reference


Schiroli D., Marraccini C., Zanetti E., Ragazzi M., Gianoncelli A., Quartieri E., Gasparini E., Iotti S., Baricchi R. & Merolle L., **Imbalance of Mg Homeostasis as a Potential Biomarker in Colon Cancer**. *Diagnostics* (2021).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