Research & Development

Upgraded Raman microscope to explore cellular origins of cancer

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Ultrafast laser tool to be developed under European project will combine artificial intelligence and endoscopy.

A European project starting this week will aim to advance laser-based coherent Raman scattering (CRS) microscopy in order to gain a better understanding of the cellular mechanisms behind the origin and progression of cancer.

Called "**CRIMSON**", the €5 million effort is being led by Dario Polli at the **Politecnico di Milano** in Italy. It also features Jena-based **Active Fiber Systems**, which will play a key role developing a turnkey, all-fiber ultrafast laser system suitable for clinical use.

The CRIMSON team says that, when combined with artificial intelligence for data analysis, the new approach will yield three-dimensional quantitative maps of sub-cellular elements in living cells and organoids, and enable fast tissue classification with "unprecedented" biomolecular sensitivity.

With a fast acquisition speed, the technique should be able to capture dynamic intra- and inter-cellular changes using time-lapse imaging, with an endoscope capable of analyzing *ex vivo* tissue samples expected by the end of the project.

Molecular fingerprints
Although the CRS technique is well established, the complexity of the laser source needed

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means that CRS systems are only currently used in specialist laboratories, rather than clinical settings.

“The laser source required for CRS is complex, expensive and needs regular alignment or maintenance, making it not suitable for biomedical research laboratories,” explains the consortium.

In addition, the CRS technique normally only measures the Raman signal at a few selected vibrational frequencies, rather than providing the kind of rich chemical information contained in spontaneous Raman, which measures the full vibrational spectrum.

Typically, that means monitoring the carbon-hydrogen stretching frequency, which produces relatively strong signals but delivers less spectroscopic information in the critical “fingerprint” region of the mid-infrared spectrum that can be used to identify specific molecules.

CRS has in fact already been shown capable of identifying metastatic brain tumors, esophageal cancer, bladder cancer, and more with a high degree of accuracy - but as well as requiring specialist knowledge, the technique tends to suffer from a slow acquisition speed.

The CRIMSON team aims to overcome these limitations, and to make broadband, hyperspectral CRS imaging much more widely accessible to biomedical researchers, through a number of critical advances.

The first of those will be the compact and alignment-free laser provided by Active Fiber Systems, alongside extending the technique for broadband operation across the fingerprint region.

Another commercial partner - the Marseille startup **Lightcore Technologies** - will develop a flexible endoscopic probe compatible with *in vivo* CRS imaging, while UK-based **Cambridge Raman Imaging** will focus on developing a scanning CRS microscope for medical and pharmaceutical applications.

"Our mission is to bring to market innovative, label-free coherent Raman technology for tumor detection and diagnosis," says CRI's Matteo Negro.

At the same time, an Italian company called **3rdPlace** will work to develop a new tissue classification technique that combines image processing with machine learning.

Immunotherapy insight

If all that hardware and software development is successful, project partners including **Jena University Hospital (JUH)**, the **Leibniz Institute of Photonics Technology (IPHT)**, and Milan’s **National Tumor Institute (INT)** will then use the improved CRS equipment to start studying cells.

At IPHT, which is home to the “Photonics4Life” biophotonics effort, researchers led by Jürgen Popp will work to develop the hyperspectral CRS approach, and begin cell and tissue imaging in the fingerprint region to unravel molecular information about cellular interaction that could have implications for cancer treatments like immunotherapy.

INT scientists will then apply the technique to learn more about thyroid cancer, for example looking at functional alterations in cells resulting from abnormalities in morphology, mass, and other characteristics.

At JUH, the focus will be on head and neck cancers specifically, with scientists there providing tissue samples and immunotherapy expertise.

Set to run through June 2024, the 42-month project hopes to revolutionize the way in which the cellular origin of disease is studied.

“Our broadband CRS microscope will extract the maximum amount of information about the biomolecular composition of the cell, coupling it with morphological information, without altering the natural state of the cell with exogenous molecules or invasive interventions,” stated the consortium partners.

• For full details of the project and all of the partners involved, visit the official **CRIMSON project web site**.

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