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Totally Integrated Linear and Non-Linear Optics Multimodal Microscopy Platform to Understand Single Cell Processes.

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A process is a sequence of events in time in which the order of events matters and can lead to different results. Cell biology relies upon spatial and time organized events where biochemistry and biomechanics play important roles. To understand cell biology working it is necessary to use tools capable of real time non-destructive observations in space and time. This means it is necessary to build an integrated multimodal platform capable to gather all available information during each one cell process, instead of a sequence of observations that require the cell process to be restarted at each modality imaging. All tools must be integrated in one instrument with the capability to acquire images simultaneously.

We are setting up such a totally integrated multimodal instrument which already includes the following microscopy techniques: multi/single photon spectral confocal, Second/Third Harmonic Generation (SHG/THG), Coherent AntiStokes Raman Scattering (CARS), Fluorescence Correlation Spectroscopy (FCS), Fluorescence Lifetime Imaging (FLIM), Förster Resonant Energy Transfer (FLIM-FRET), confocal Micro-Raman spectroscopy, Multiple Optical Tweezers, Laser Microdissection and, finally, a tip-enhancement/Atomic Force Microscopy near field optical microscopy.

Optical Tweezers and tip-enhancement/AFM are somehow different from the other techniques because they allow the direct interference on the cell processes, and not only to observe them. They also open the way to perform bio-mechanical measurements, while near field allowed us to perform super resolution 10-20 nm spatial resolution microscopy. Raman and CARS provide chemically selective information in time and space. CARS microscopy can acquire images at video rate, 30 frames per second. AFM/Tip-enhancement provides chemical selective information with 10 nm spatial resolution. SHG is great to see collagen fibrils, among other cell tissue structures, an important feature in tissue architecture, especially in cancers. THG can highlight cell nuclei and lipid droplets. FLIM is sensitive to the molecular chemical environment around fluorophores. FRET is an event marker. FCS is sensitive to very low concentrations of

chemicals and can be used to follow chemical reactions and to measure the molecule´s hydrodynamic radii.

We will describe the setup of such a system and provide examples of the use of this multimodal integrated tool. This platform is not only available for the life-science research community but is also being used to accelerate the learning curve of how to use all these techniques to extract the most relevant dynamical cell biology information.