Mapping drug mechano-sensitivity in tumour spheroids with brillouin light scattering

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Aims and/or Background: Mechanical properties are key players in tumour physiology, but their exact role in growth, invasivity and response to drugs remains largely unknown due to the lack of characterisation techniques. Standard microscopy techniques are limited by the photon mean free-path in the imaging depth they can achieve to ~100 μm. Besides, the use of fluorophores or tags alters normal cell functions and eventually kills cells, hindering the study of drug kinetics over standard therapeutic time scales. Most importantly, they provide a contrast that does not reveal mechanical properties. In this work we implement a novel quantitative, label-free microscopy technique based on Brillouin light scattering (BLS) to decipher the link between mechanical properties and drug efficacy.

Methods: To understand the physics of tissues and to accelerate the translation of novel therapeutics to the clinic, it is necessary to define biological models that recapitulate closely the complex mechanics of tumours. Multicellular spheroids (MS) are an apt tumour model that captures the spatial gradient distribution of mechanics and biological factors, and resistance to drug penetration. For demonstration, we monitored with BLS the mechanical properties of MS formed from a colorectal cancer cell line HCT116 during a 3-days chemotherapy with 5-fluorouracil (5-FU).

Results: We captured BLS maps with 10 μm resolution in the equatorial plane of the MS to probe the distribution of mechanical properties and monitor in-depth drug sensitivity. Our images reveal a clear variation in the rigidity and viscosity from the outer rim to the core of the untreated MS. In addition, the mechanics across the centre of the spheroid during the 5-FU therapy show the radial action of the drug starting in the outer regions of the MS from the first day of exposure to reach the core in about 3 days. This observation is consistent with live/dead assays by epifluorescence microscopy.

Conclusion: Such results, which cannot be observed by any other existing modality, demonstrate the ability of BLS to image quantitatively drug efficacy on *in vitro* models using mechanical properties as the contrast mechanism, without tags, and with an unprecedented imaging depth in ~300-500 μm objects. Our approach should shed light on the link between mechanics, structure and biological functionality, thereby offering innovating solutions for the understanding and control of tumors and design of anti-cancer drugs.