Inorganic Deep-Tissue Self-Lighting PhotoDynamic Therapy: "Simple and Scalable"

In our conversation, Luigi described his research group's innovation of a CeF_3-ZnO scintillating nanocomposite as "simple and scalable". I am speaking of Associate Professor Luigi Cristofolini of the Physics and Earth Science Department, University of Parma, Italy. The framework for this research was provided by the early works of Professor Wei Chen at University of Texas at Arlington [Juzenas, 2008]. In 2015, as part of the dissemination effort of an interdisciplinary project led by Dr. Giancarlo Salviati (IMEM/CNR, Parma, Italy), Luigi co-authored "Porphyrin conjugated SiC/SiOx nanowires for X-ray-excited photodynamic therapy", which appeared in Scientific Reports published by Nature [Rossi, 2015]. The work featured in our Journal (access free download here) contributes to establishing a new paradigm in nanostructures intended for photodynamic therapy (PDT) – the irradiation activation of inorganic scintillating nanocomposites to produce single oxygen species shown to induce oxidative stress, leading to cell death.

The primary interest in deep tissue self-lighting photodynamic therapy (SLPDT) is its application in deep cancer treatment by low doses of X-rays. Current PDT capabilities applied to cancer treatment are limited to skin surface or near-surface treatments. The ideal SLPDT must offer the benefit of a chemical and functional structure that displays: (1) excellent cellular uptake; (2) excellent chemical stability in biological environments; (3) low cytotoxicity in dark; and (4) the ability to produce reactive species such as singlet oxygen and other radicals upon X-ray irradiation. Initial evaluation of CeF_3-ZnO scintillating nanocomposites appears encouraging. Luigi shared with me that both PDT and SLPDT are inherently local treatments due to the very short (3-4 us) lifetime of singlet oxygen. This means that any successful molecule/nanostructure/nanodevice solution has to be located within 100-200 nm of the target tumor. Several classes of nanosystems have been proposed in the literature as effective agents for SLPDT, including nanoparticles, nanofibers, and nanowires.

To this stage, Luigi and his group have been able to demonstrate the chemical cascade process in which the photosensitive ZnO is activated when the scintillator CeF_3 is irradiated with UV light. Further, the group demonstrated the sub-micrometer size of the nanocomposite, which ensures the necessary diffusive profile, together with positive cellular uptake and optimal cytocompatibility in the absence of any excitation. The nanocomposite, therefore, will be released in the circulation, and will reach the target site where it will be able to diffuse into the cell. This process will be followed by the X-ray excitation protocol that initiates the chemical process leading to the death of the tumor cell through oxidative stress.

While these results are encouraging, the group still needs to evaluate several aspects. The generation of the needed oxygen species is critical to inducing oxidative stress. Irradiation at 325nm is critical because it allows assessment of the optical coupling between CeF_3 and ZnO, which is expected to lead to the production of singlet oxygen species. While the literature appears to validate this process, it still requires direct confirmation that CeF_3-ZnO scintillating nanocomposites can generate the singlet oxygen species. The PDT effect in inducing cellular death of the targeted tumor cells upon X-ray irradiation of uptaken nanostructures must also be investigated. Further, the group plans to functionalize the CeF_3-ZnO scintillating nanocomposites with homing molecules capable of selectively targeting the tumor location.

Every innovation must withstand the burden of comparative analysis. Therefore, I asked Luigi to briefly discuss how the group's innovation compares to existing PDTs. He first described the importance of shape and size of the CeF_3-ZnO scintillating nanocomposite. Nanowires and nanotubes are relatively long objects. Therefore, they have low diffusivity and cannot be delivered through the circulatory system at a therapeutically relevant concentration. In contrast, nanoparticles, such as CeF_3-ZnO scintillating nanocomposite, tend to diffuse easily and, if functionalized with suitable targeting molecules, could target specific tissues or specific tumor cells once released into the circulatory system. The efficacy of CeF_3-ZnO scintillating nanocomposite is expected to be superior (but yet to be fully demonstrated) to current solutions. The superiority in efficacy is owed to the innovative idea of growing the photoactive component directly onto the scintillating material. As reported in the literature, this approach should lead to superior generation of the desired single oxygen species. In contrast to organic based solutions, this innovation consists of inorganic materials, unlikely to degrade by X–ray or in biologic media. A very real problem with other solutions is the possible leakage of the organic photosensitizer into the biological environment, whereas the CeF_3-ZnO scintillating nanocomposite has already demonstrated superior cytocompatibility. Most importantly, as Luigi emphasized, the innovation itself is a "simple and scalable production route, based on a two-step chemical synthesis".

We are very much looking forward to the strategic validation of the CeF_3-ZnO scintillating nanocomposite as a route to a viable cancer treatment solution where, presently, there is little hope of treatment efficacy. I would like to thank Associate Professor Cristofolini and his colleagues for kindly agreeing to offer an in depth investigational account of their ongoing work. Additional information on the focus of this research can be found at: http://www2.difest.unipr.it/?q=node/97.

To our readers: I am looking forward to your comments that can be sent to gabriela.voskerician@case.edu using the heading “Editors’ Choice”. We hope to develop this feature into a dynamic forum think-tank.

Bibliography:

Juzenas P, Chen W, Sun YP, Coelho MA, Generalov R, Generalova N, Christensen IL. Quantum dots and nanoparticles for photodynamic and radiation therapies of cancer. Adv Drug Deliv Rev. 2008 Dec 14;60(15):1600-14.

Rossi F, Bedogni E, Bigi F, Rimoldi T, Cristofolini L, Pinelli S, Alinovi R, Negri M, Dhanabalan SC, Attolini G, Fabbri F, Goldoni M, Mutti A, Benecchi G, Ghetti C, Iannotta S, Salviati G. Porphyrin conjugated SiC/SiOx nanowires for X-ray-excited photodynamic therapy. Sci Rep. 2015 Jan 5;5:7606.