New Graphene Pharmaceutical Formulations for Phototherapy of Skin Cancer: *in vitro* validation and *ex-vivo* human skin permeation studies

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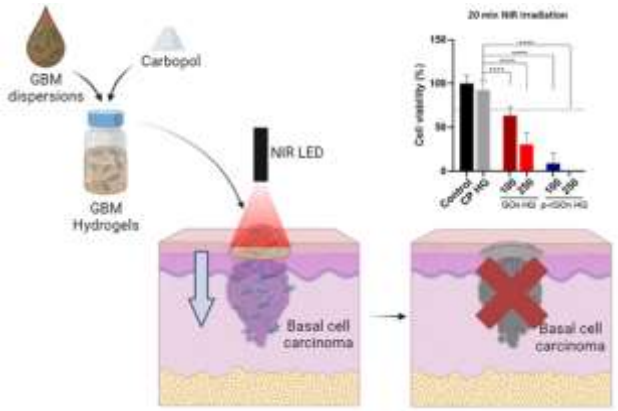

Basal cell carcinoma (BCC) is the most common form of human cancer, and treatment usually involves surgery. However, several non-invasive strategies such as photothermal therapy (PTT) have been explored. Graphene-based materials (GBMs) are good candidates to act as photothermal agents since they can absorb near-infrared (NIR) light energy that can induce hyperthermia, leading to tumour cells apoptosis [1]. In this study, we proposed the use of nanographene oxide (GOn) and partially-reduced graphene oxide (p-rGOn) as platforms for photothermal therapy of BCC. GO was produced through the modified Hummers method, and further ultrasonicated to obtain GOn. GOn was then photo-reduced to p-rGOn, a new water stable material recently developed at our laboratory using an innovative industrially scalable process. Both materials were incorporated in carbopol hydrogels (HG) to produce pharmaceutical formulations that could be administered to patients skin, and characterized physical-chemically. GBMs were obtained with mean lateral dimensions of 216 ±77 nm (GOn) and 206 ±107 nm (p-rGOn). GOn and p-rGOn HG showed zeta potential values of -49.2 ±3.4 and -50.0 ±3.3 mV, respectively. After 30 min irradiation with a near-infrared photothermal therapy lamp source (15.70 mW cm^{-2}), GOn HG increased temperature to 45.7 °C, while p-rGOn HG reached 48.2 °C. GBM HG (250 µg mL^{-1}) have been shown not to affect human skin fibroblasts (HFF-1) morphology or viability. Therefore, GBM HG photothermal effect was tested towards a human squamous carcinoma cell line (A-431). After 20 min irradiation, p-rGOn HG (250 µg mL^{-1}) completely eradicated cancer cells, confirmed through cell viability and immunocytochemistry studies. GBM HG *ex vivo* human skin permeability (from a healthy patient, S. João Hospital, Porto) was evaluated using a Franz cell system. Materials were capable of permeating across skin in a time-dependent manner. After 6 h of skin contact, 71.7 % or 83.9 % of GOn or p-rGOn, respectively, reached the receptor compartment, which means that a tumour could be topically infiltrated with the materials. This is the 1st pharmaceutical formulation ever reported to deliver graphene through skin for cancer therapy. *In vivo* studies are ongoing.

References

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