Profiling a Prophylactic Local Triple Therapy Hydrogel Patch to Treat and Prevent Cancer Recurrence

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Statement of Purpose: Colorectal cancer (CRC) is the third most common cancer found in the US as specified by the American Cancer Society. Conventional cancer therapies involve the systemic employment of anticancer agents following tumour resection that do not discriminate between cancer and normal cells and pose the risk for cancer recurrence. Here, we developed a new technology based on a prophylactic hydrogel patch for local cancer therapy using triple combination therapy: gene, drug and phototherapy. In vivo data in colon cancer mouse model revealed that the triple therapy washout procedure (i.e. gene, chemo and photo therapies) completely abrogated tumour recurrence following tumour resection. The application of these hydrogel patches to tumours without resection resulted in complete tumour remission, thus eliminating the need for resection.

Methods: The tumour was coated with a nanocomposite adhesive hydrogel patch, based on dendrimer:dextran that provides with local delivery of embedded spherical and rod-shaped gold nanoparticles. The spherical-shaped nanoparticles were used as a first wave of treatment to deliver siRNAs against a key oncogene driver (Kras), and the rod-shaped nanoparticles afforded phototherapy and drug delivery, as near-infrared (NIR) radiation is converted into heat causing local drug release and cell damage. Synthesis and characterization of the material can be found in the published paepr[1]. Dynamic light scattering and zeta potential were used to characterize the nanoparticles, fluorescence and UV/Vis Spectroscopy for uptake experiments and environmental scanning microscopy and High-resolution Cryo-TEM to identify scaffold morphology.

Results: The triple therapy (i.e. gene, chemo and photo therapy combination) was initially used as a neoadjuvant therapy to shrink the tumor prior to resection (Fig. 1a-b). Application of the hydrogel patch resulted in complete tumour abrogation, eliminating the need for resection. Material application following resection prevented colon cancer recurrence, unlike the sham group, in which 40% of the tumours recurred following resection (Fig. 1c-d). In fact, when the patch was used as a prophylactic measure following tumour resection, complete remission was achieved. Our results demonstrate the superiority of the local administration when compared to systemic and intratumoral injections (not shown here)[1]. Detailed pathway analysis were used to identify the molecular pathways and describe the biological processes of the transcript profiling data behind the three therapeutic modalities, photo-, gene- and chemo-therapy by tumour gene expression profiling in treated mice. We found that altered genes belong to multiple pathways, mainly related with metabolism, intracellular transport mechanisms, receptor signaling, extracellular matrix, cell cycle and apoptosis, immune and defense response and transcription/ translation processes.[1] Tumour genetic profiles of mice treated with the triple therapy completely changed over time and are associated with an increased number of altered genes, which correlates with the maximum therapeutic efficacy observed in the evaluation of the tumour size.

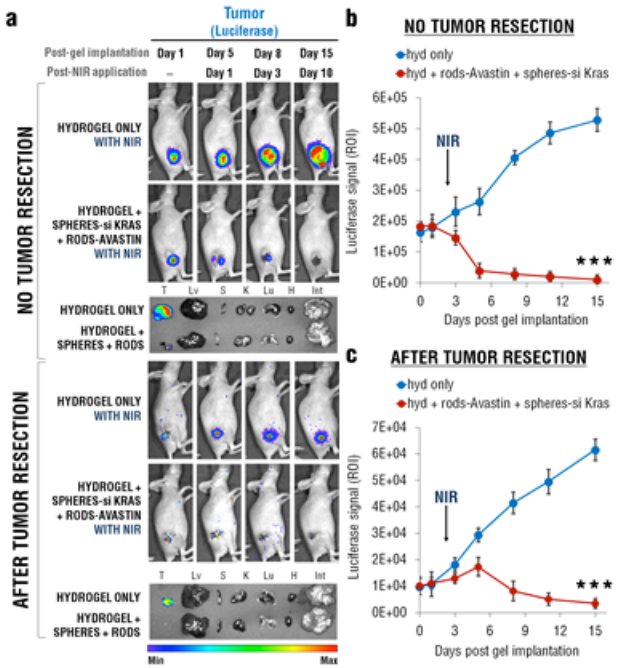

Figure 1. (**a**) Live imaging of SCID mice with colorectal tumour xenografts implanted with hydrogels embedded with drug gold nanorods and siRNA gold nanospheres with NIR treatment with no tumour resection and after tumour resection (n=5 per group). Ex vivo images of tumours and whole body organs are presented. Luciferase activity representing tumour burden following treatment with no tumour resection (**b**) and after tumour resection (**c**) (n=5, statistical analysis performed using a two-way analysis of variance ANOVA, ***, P<0.001).

Conclusions: Local triple therapy shows high promise in the treatment of colon cancer owing to improved delivery efficiency and the synergistic effect of the three therapeutic modalities. This system can be adapted to target any cancer cell type and molecular targets that are associated with disease progression and related to how tumors respond to each therapeutic modality.

Reference: 1. J. Conde, N. Oliva, Y. Zhang and N. Artzi, Nature materials, 15, 1128, 2016.