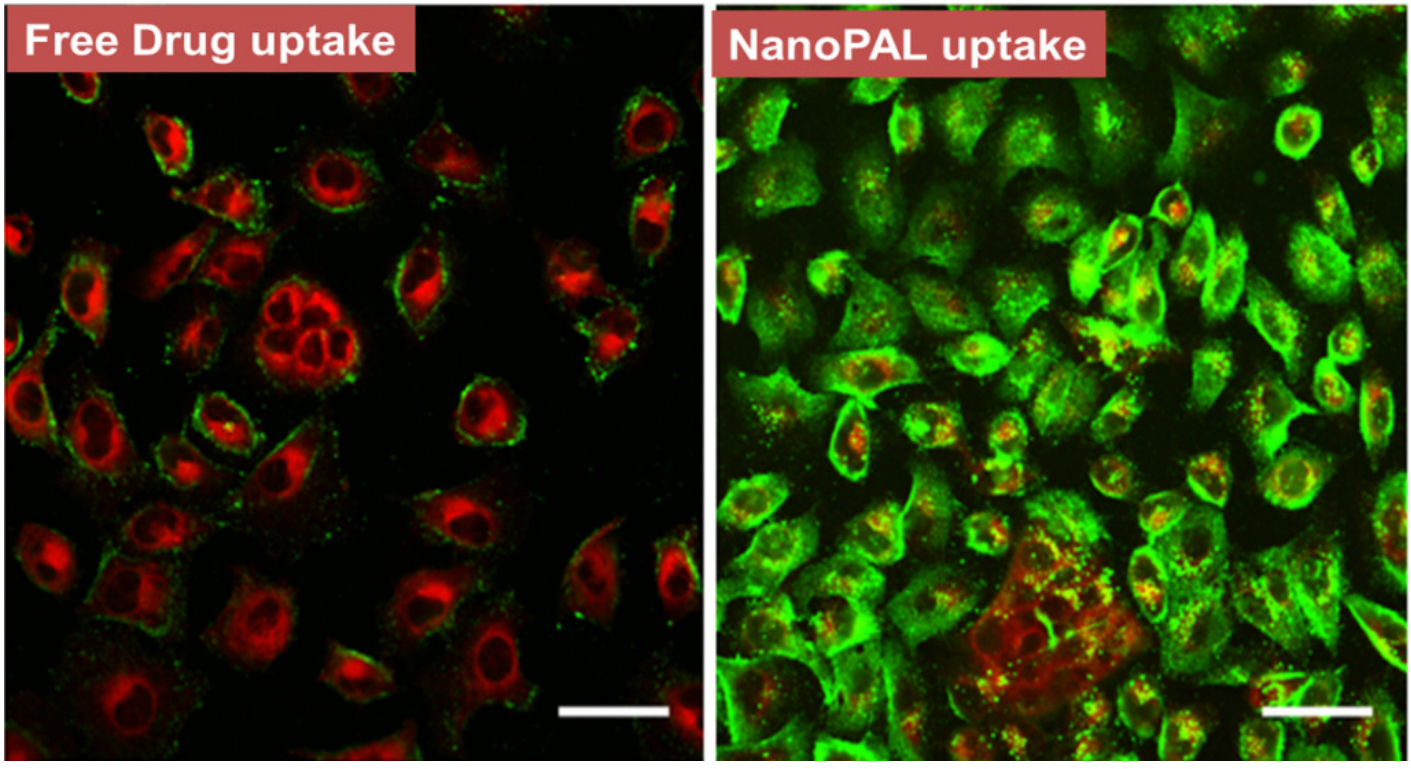
Using nanotechnology to outsmart pancreatic cancer

Cancer is a versatile disease and makes use of complex cellular signaling networks to defend itself against a host of treatments. Pancreatic cancer in particular has proven challenging with tenacious resistance to DNA-damaging chemoradiation. Malignant cells disobey the normal ‘rules’ of self-regulated growth and death and use cellular signaling pathways to resist and survive the therapy. A major challenge in cancer therapy is to mop up the cytokines, the growth factors that are secreted by tumor cells, which play a major role in instigating strategies to escape from these treatments. Targeting the tumors by combining and delivering two or more therapies simultaneously in a ‘smart’ vehicle, is a viable response to the above challenges.

Researchers at the Wellman Center for Photomedicine, Massachusetts General Hospital and Harvard Medical School have done just that, designing a smart nanoparticle, nanoPAL. These 120 nm nanoparticles can successfully carry the payload of therapeutic antibodies and release within the tumor environment to neutralize secreted cytokines in concert with a potent phototherapy effective against drug-resistant pancreatic cancer cells. This new nanotechnology was developed in the lab of Dr. Tayyaba Hasan, Professor of Dermatology at the Wellman Center and a Professor of Health Sciences and Technology (Harvard-Massachusetts Institute of Technology), and is described in the recent publication in journal Nanomedicine: Nanotechnology, Biology and Medicine.



The cancer cells in the confocal images above show the uptake pattern of the two drugs, the

photosensitizer (red) and the anti-VEGF antibody (green). The drugs delivered as conventional cocktail (on the left) show minimal antibody uptake, where as a custom-designed nanoPAL delivery shows a significant increase in the availability of the drugs inside the cell. Scale bars, 20 um.

“Our laboratory has been exploring the use of photodynamic therapy, called PDT for short, in clinical trials as a first line treatment of human pancreatic cancer with promising efficacy and safety results, and the next step is to develop nanoparticles to co-deliver combination therapies that enhance and synergize with PDT to prevent local recurrence and to attack metastases,” said Hasan. “Photodynamic therapy uses energy provided by near infrared light to excite nontoxic photosensitizing molecules that go on to create cytotoxic reactive species that kill the cancer tissue. This light-activated approach bypasses cell death signaling checkpoints in drug-resistant cancer cells, and synergizes with chemotherapy to efficiently kill pancreatic cancer cells.”

However, even with enhanced efficacy provided by photodynamic therapy, the tumors often switch to specific survival pathways post-treatment and promote tumor recurrence. In fact, this is a broad problem for virtually all modes of cancer therapy. The vascular endothelial growth factor (VEGF) signaling pathway is an archetypical example of an escape mechanism from photodynamic, chemo- and radiotherapy treatments. Upregulation of tumor VEGF secretion supports tumor vessel regrowth for proper nourishment, maintenance of a supportive tumor microenvironment and cancer cell survival, post-treatment. The survivor cancer cells give rise to recurrence, often comprising cell populations with increased resistance to subsequent therapies and thus present a formidable target for the next round of therapy. “We rationalized that co-delivery of an anti-VEGF antibody (bevacizumab) with the photodynamic agent would facilitate an optimal combination therapy where the antibody is present at the right place and time to effectively mop up a burst in VEGF secretion within the tumor microenvironment—helping to prevent regrowth of persistent cancer cell populations,” Hasan explained.

“To realize simultaneous photodynamic and anti-VEGF therapy, we designed and optimized a nanotechnology based system, termed nanophotoactivatable liposomes (nanoPALs) that co-package and co-deliver the combination therapy,” said Dr. Shifalika Tangutoori, postdoctoral fellow in the Hasan lab and first author of the paper. “The superior tumor accumulation in principle can be attributed to ‘Enhanced Permeation and Retention’ effect. The nano-scale size and the slightly positive surface charge of the nanoPAL aids in its easy escape from the tumor blood stream and facilitates electrostatic interactions with the negatively charged, leaky tumor vasculature, after which, the sluggish tumor microenvironment retains the nanoPAL for a significantly longer time in the tumor tissues.” Optimization of photodynamic and anti-VEGF agent co-loading into the nanoPAL, as well as fine-tuning of the size and surface charge, were thus performed to preserve potencies of the drugs and to promote tumor accumulation and cellular uptake. The nanoPALs were efficiently taken up by the cancer cells and intracellular delivery of the antibody was apparent—potentially enabling the neutralization of the VEGF pools inside the cancer cells prior to

their secretion and systemic release. Furthermore, these nanoPALs were custom-designed to disintegrate upon laser irradiation to facilitate a burst release of the photosensitizer and antibody cargo.

This new nanotechnology platform was tested in pancreatic tumor bearing mice injected with either nanoPALs or a cocktail of the conventional pharmaceutical formulations of the two agents. Remarkably, nanoPAL treatment resulted in nearly complete disappearance of the tumor, whereas the group injected with the conventional cocktail (at the same equivalent dosages loaded into the nanoPAL), only managed to temporarily stabilize tumor growth without a reduction in tumor burden. “We attribute this to the importance of molecular signaling spatiotemporal dynamics in utilizing targeted therapies to successfully achieve multi-agent interactions,” said Dr. Bryan Spring, postdoctoral fellow in the Hasan lab and a co-author of the study. “This study shows that simply combining drugs into a cocktail is suboptimal, and consideration of optimal delivery platforms and sequences leads to enhanced outcomes.”

Publication

Simultaneous delivery of cytotoxic and biologic therapeutics using nanophotoactivatable liposomes enhances treatment efficacy in a mouse model of pancreatic cancer.
Tangutoori S, Spring BQ, Mai Z, Palanisami A, Mensah L, Hasan T
Nanomedicine. 2015 Sep 25