Targeting intracellular VEGF using nanotechnology for subcellular delivery of bevacizumab improves efficacy of combination therapy against pancreatic cancer

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Objective: To study the efficacy of neutralizing the intracellular VEGF using nanotechnology-based delivery of bevacizumab (Avastin) in combination with a light-based cytotoxic therapy in an *in vivo* orthotopic pancreatic cancer (PanCa) model.

Rationale: Avastin, a monoclonal antibody against vascular endothelial growth factor (VEGF), have been approved for many cancers. Recent findings suggest the existence of an intracellular VEGF pool which cannot be neutralized by conventional delivery of Avastin. Inhibiting the intracellular VEGF pool may lead to a better treatment response than the conventional strategy. The intracellular VEGF pool can be neutralized through the intracellular delivery of Avastin by using nanotechnology. PanCa is highly resistant to cytotoxic therapies and few patients are candidates for surgical intervention. Photodynamic therapy (PDT), a photochemistry based modality, has demonstrated promising results in treating PanCa. PDT often bypasses the resistance mechanism of chemotherapy and radiotherapy. PDT is known to sensitize cancers to anti-VEGF therapy. Simultaneous delivery of multiple agents in a single nano-construct could improve the treatment response of combination therapies.

Methods: We investigated the effect of neutralizing intracellular VEGF using nanotechnology for co-delivery of Avastin and a PDT agent in AsPC-1 *in vitro* and an orthotopic *in vivo* pancreatic cancer mouse models. For this we explored the use of a new construct called “nanocells” in which the PS was non-covalently trapped inside polymer nanoparticles and these, along with Avastin, were then encapsulated inside liposomes.

Results: *In vitro*, nanocells containing Avastin (NCA) delivered Avastin intracellularly and this significantly enhanced the cytotoxicity in AsPC-1 cells. NCA based PDT also significantly improved the acute treatment response in mice that were orthotopically implanted with human pancreatic tumors. Avastin delivered extracellularly with PDT did not show much improvement. NCA-based treatment also significantly reduced the occurrence and extent of metastasis to distal organs like liver, lungs and the lymph nodes.

Conclusions: We propose a new paradigm for Avastin-based therapy by combining intracellular delivery of Avastin with PDT using nanotechnology for the treatment of PanCa. This suggests the involvement of an intracellular VEGF signaling pathway that plays an important role in cancer cell survival, proliferation and migration following PDT. Encapsulation of Avastin may drastically reduce the serious side effects associated with the drug which have recently come to light while significantly improving its efficacy. This could have a major clinical impact on diseases that are currently being treated with Avastin.