Noninvasive Radiofrequency Field Destruction of Pancreatic Adenocarcinoma Xenografts Treated with Targeted Gold Nanoparticles

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Abstract

Purpose: Pancreatic carcinoma is one of the deadliest cancers with few effective treatments. Gold nanoparticles (AuNP) are potentially therapeutic because of the safety demonstrated thus far and their physiochemical characteristics. We used the astounding heating rates of AuNPs in nonionizing radiofrequency (RF) radiation to investigate human pancreatic xenograft destruction in a murine model.

Experimental Design: Weekly, Panc-1 and Capan-1 human pancreatic carcinoma xenografts in immunocompromised mice were exposed to an RF field 36 hours after treatment (intraperitoneal) with cetuximab- or PAM4 antibody–conjugated AuNPs, respectively. Tumor sizes were measured weekly, whereas necrosis and cleaved caspase-3 were investigated with hematoxylin–eosin staining and immunofluorescence, respectively. In addition, AuNP internalization and cytotoxicity were investigated in vitro with confocal microscopy and flow cytometry, respectively.

Results: Panc-1 cells demonstrated increased apoptosis with decreased viability after treatment with cetuximab-conjugated AuNPs and RF field exposure (P = 0.00005). Differences in xenograft volumes were observed within 2 weeks of initiating therapy. Cetuximab- and PAM4-conjugated AuNPs demonstrated RF field–induced destruction of Panc-1 and Capan-1 pancreatic carcinoma xenografts after 6 weeks of weekly treatment (P = 0.004 and P = 0.035, respectively). There was no evidence of injury to murine organs. Cleaved caspase-3 and necrosis were both increased in treated tumors.

Conclusions: This study demonstrates a potentially novel cancer therapy by noninvasively inducing intracellular hyperthermia with targeted AuNPs in an RF field. While the therapy is dependent on the specificity of the targeting antibody, normal tissues were without toxicity despite systemic therapy and whole-body RF field exposure.
noselects that systemic delivery of antibody targeted gold nanoparticles (AuNPs) would induce hyperthermic cytotoxicity after RF field exposure in human pancreatic carcinoma xenografts without injury to normal tissues. Antibodies to 2 distinct human antigens (EGFR-1 and MUC-1) were utilized to deliver 2 AuNPs of different sizes to 2 unique human pancreatic xenografts. Although EGFR-1 is a problematic therapeutic target due to its diverse constitutive expression in normal tissues, PAM4 is a human antibody to MUC-1 that is specific to pancreatic carcinoma (18). The components were chosen such that the constructs had similar sizes that could lead to increased tumor internalization rates (19). The primary aim was to show human pancreatic cancer xenograft destruction.

**Materials and Methods**

**Cell culture, antibodies, fluorophores, and gold nanoparticles**

Two human pancreatic carcinoma cell lines, Panc-1 and Capan-1, were acquired from the American Type Culture Collection (ATCC) confirmed by the Characterized Cell Line Core Service (M. D. Anderson Cancer Center; December 2009), and maintained according to ATCC’s cell media recommendations in standard conditions (37°C, 5% CO2). All experiments utilized standard cell culture coated dishes and equipment (BD Biosciences; Corning Inc.). Cetuximab (C225; Bristol-Myers Squibb), a chimeric monoclonal IgG1 antibody against human EGFR-1 was conjugated to spherical 10-nm AuNPs (Ted Pella, Inc.) via a linker. PAM4 (Immunomedics, Inc.), a human monoclonal antibody against a mucin glycoprotein, MUC-1, was directly conjugated to 20-nm AuNPs (Ted Pella, Inc.) via a thiol–gold bond described later. All fluorophores or fluorophore conjugates were used as directed by the manufacturer (Invitrogen Corp.).

**AuNP constructs and characterization**

C225 was conjugated via covalent hydrazide-thiol heterobifunctional linker (Sensopath Technologies, Inc.) from a previously published protocol with slight modifications based on glycosolation of the Fc region (20). Briefly, a solution of 10-nm AuNPs were twice washed in a borate buffer solution at pH 8. A total of 450 μg of C225 with linker was slowly added to a 1,000 μg of AuNP solution. It was placed on a continuous mixer and incubated at room temperature for 4 hours. Next, the conjugate was concentrated 15-fold in a 50,000 molecular weight centrifugation filter unit (Millipore Corp.) at 3,800 × g.

Because PAM4 does not have the same glycosolation status in the Fc region as C225, it was directly conjugated to slightly larger AuNPs without a linker via a thiol–gold interaction. First, PAM4 IgG was washed in borate buffer (pH 8) twice and resuspended at a concentration of 2 mg/mL. A monovalent, single-molecule IgG (Fc + Fab with reactive sulfur groups on the heavy chain formerly of the disulfide bond) was created by reducing the interchain disulfide bond at the hinge region with 3 molar excess of tris(2-carboxyethyl)phosphine, which is a relatively gentle, but very specific, nonsulfur-containing disulfide bond reducing agent that does not reduce heavy-light intrachain disulfide bonds or internal disulfide bonds at the antigen binding site at these concentrations (21). Subsequently, 450 μg of “activated” PAM4 was mixed with 1,000 μg of 20-nm AuNP in borate buffer and mixed for 4 hours in the dark at room temperature to permit the reduced sulfur moieties to directly form thiol–gold bonds on the AuNPs. The construct was twice washed with borate buffer, concentrated 15-fold in a 50,000 molecular weight centrifugation filter unit (Millipore Corp.) at 3,800 × g.

A small shift in the peak plasmonic absorbance of the AuNPs (NS1; Applied NanoFluorescence) was indicative of a nonaggregated conjugation state after challenge with equivolume of 10% sodium chloride (21). Dynamic light scattering (DLS; Horiba, Ltd.) determined the average hydrodynamic diameter of the constructs (500 measurements per sample in triplicate).

**Target protein expression in Panc-1 and Capan-1 cells with immunoprecipitation**

The cell membrane expression of EGFR-1 and MUC-1 was confirmed by Western blot analysis. Briefly, cell pellets were lysed with cold radioimmunoprecipitation assay buffer and centrifuged at 13,000 rpm for 30 minutes. The protein extracts (30 μg per lane) were electrophoresed on Bis-Tris protein gel, transferred to a polyvinylidene difluoride membrane, and sequentially incubated in 5% dry milk and primary antibodies (BD Biosciences and Immunomedics, Inc.). Next, the membranes were incubated with secondary anti-human IgG antibodies (H + L chains; Jackson ImmunoResearch, West Grove, PA). Images were acquired by a high-resolution photoscanner (CanoScan 4400F;
Confocal imaging of antibody-conjugated AuNPs in vitro

Confocal images were prepared by growing Panc-1 cells on standard 1.5 glass cover slips, which were treated with AlexaFluor (AF) 647–labeled C225 (the primary antibody delivered to living cells). 10-nm AuNP alone, the labeled C225-AuNP–conjugated construct, or neither for 3 hours. Cell membranes were stained with 5 μg/mL of wheat germ agglutinin conjugated to AF 594 (Invitrogen Corp.) by incubating the cover slip for 10 minutes at 37°C. After phosphate buffered saline (PBS) washings, the cells were fixed with 4% paraformaldehyde and permeabilized with cold 100% methanol. Blocking was performed for 1 hour with blocking solution (3% bovine serum albumin (BSA) + 1% animal serum in PBS). Cells were washed and stained with AF 488–labeled secondary antibody against the heavy and light chains of human IgG (Invitrogen Corp.). After washing, DNA was stained with 4',6-diamidino-2-phenylindole dihydrochloride (DAPI; 300 nmol/L) for 5 minutes. Cover slips were mounted (Dako Denmark A/S, Glostrup, Denmark), dried, sealed, and stored in the dark at 4°C until analyzed (Olympus DSU with Orca II ER camera; Olympus America Inc., Center Valley, PA).

In a separate experiment, Panc-1 cells were treated with AF 647–labeled C225 at the same concentration with or without AuNPs to determine the percentage of cells in vitro with measurable amounts of primary fluorophore–labeled C225-AuNP. Cells were identified in the usual manner by an automated cytometer while the fluorescence of AF 647–labeled C225-AuNP–conjugated construct, or neither for 3 hours. Separate groups (n = 4 each) underwent RF field exposure at 600 W for 10 minutes. Bulk media temperature remained between 36°C and 41°C, as measured by an IR camera (FLIR SC 6000). Viability was measured with flow cytometry (LSRII; BD Biosciences) 36 hours after exposure. Briefly, cell media (i.e., dying cells that were floating) was collected and the adherent remaining cells were released with trypsin. The trypsin was then neutralized with cell media and the cells were collected. Each sample was washed and stained without fixation or permeabilization. After a final wash, 50,000 cellular events were acquired for each sample and analyzed with FlowJo 8.8.6 (TreeStar, Inc.).

Panc-1 in vitro RF field exposure and cytotoxicity after C225-AuNP treatment

Panc-1 cells were plated in quadruplicate at a concentration of 1 × 10⁶ cells/mL in 60-mm dishes and incubated overnight. Negative controls remained untreated, whereas the others were treated with C225 alone or C225-AuNP. Separate groups (n = 4 each) underwent RF field exposure at 600 W for 10 minutes. Bulk media temperature remained between 36°C and 41°C, as measured by an IR camera (FLIR SC 6000). Viability was measured with flow cytometry (LSRII; BD Biosciences) 36 hours after exposure. Briefly, cell media (i.e., dying cells that were floating) was collected and the adherent remaining cells were released with trypsin. The trypsin was then neutralized with cell media and the cells were collected. Each sample was washed and stained without fixation or permeabilization. After a final wash, 50,000 cellular events were acquired for each sample and analyzed with FlowJo 8.8.6 (TreeStar, Inc.). After gating the single cell population, Annexin V, a protein that binds to membrane protein phosphatidylserine, positive cells were considered apoptotic; whereas propidium iodide (PI), a chemical that fluoresces when bound to DNA, positive cells were considered necrotic. Annexin V and PI double-positive cells were considered dead cells, whereas double-negative cells were characterized as viable.

Panc-1 and Capan-1 pancreatic xenografts AuNP treatment and RF field exposure

Nude balb/c mice (NCI Mouse Repository) were subcutaneously injected with 3 × 10⁶ Panc-1 or Capan-1 cells to the right flank (n = 20 each cell line). After the tumors were palpable (approximately 3 weeks), mice within each cancer cell type were randomly assigned to 1 of 4 groups. The mice with Panc-1 xenografts were treated/exposed to no treatment, C225-AuNP without RF exposure, RF expo-
ure alone, or C225-AuNP treatment plus RF exposure. The mice were treated with C225-AuNP at 10 mg/kg by gold weight injected intraperitoneally to prevent AuNP collection at the site of an extremity (i.e., tail vein). RF exposure consisted of 600-W generator power for 10 minutes with an air gap of 10 cm. All antibody-AuNP treatments occurred weekly, whereas all RF exposures occurred 36 hours after treatments on a weekly basis. Tumors were measured 48 hours after RF exposure each week, whereas C225-AuNP treatment and RF exposure began after week 1.

Mice with Capan-1 tumors were randomly assigned to 1 of 4 groups as well (n = 5 each group). Those groups were untreated control, PAM4-AuNP treatment only, unconjugated AuNP treatment plus RF field exposure (600-W generator power, 10-minute duration, and 10-cm air gap), and PAM4-AuNP treatment weekly with the same RF exposure weekly. Unconjugated AuNP and PAM4-AuNP were also treated intraperitoneally at 10 mg/kg by gold weight for each.

During the experiment, all mice were kept in accordance with an Institutional Animal Care and Use Committee approved protocol. To safely expose the animals to RF fields, their tails, ears, and paws were completely grounded to avoid excess current in the extremities that would result in electrothermal injuries. This was accomplished by placing mice directly on a large grounded copper plate and attaching conducting copper tape (3M) to the extremities and plate.

Mice were sedated with ketamine 0.1 mg/g and xylazine 0.01 mg/g intraperitoneally prior to each RF field exposure and monitored thereafter. The temperature of each mouse was continuously measured with an IR camera (FLIR SC 6000), and at no time did the temperature exceed 41.5°C. For the first minute of every RF field exposure, a cuvette with 100 µg/ml of 20-nm AuNPs was placed within 1.5 cm of the tumor. This served as the control to confirm heating of AuNPs in the RF field. After 1 minute, the RF field generator was briefly turned off (<2 seconds) to remove the cuvette, as it approached boiling temperatures soon thereafter.

Tumor volumes (width squared \times length) were measured weekly with electronic calipers. After 6 weeks of treatment, the animals were euthanized and selected organs (liver, spleen, kidney, lung, and tumor) were harvested for gold biodistribution and histopathologic evaluation. For evaluation of normal organ and tumor-specific injury, specimens were prepared for histologic procedures, embedded in paraffin, and sectioned at 5 µm. The sections were stained with hematoxylin and eosin stain (H&E) and examined by light microscopy. Injury was assessed by grade (grade 1: rare with hematoxylin and eosin stain (H&E) and examined by light microscopy. Injury was assessed by grade (grade 1: rare

\[ \text{peak plasmonic absorption} \]
nalized faster than antibody-conjugated AuNPs. In a separate experiment, fluorescence from a fluorophore directly attached to C225 showed significant overlap in vitro to secondary antibodies conjugated to a different fluorophore, suggesting most of the primary antibody remains intact even after internalization (Fig. 3). Nearly 90% of cells contain measurable C225-AuNPs based on direct fluorescence labeling (Fig. 3; \( P < 0.0001 \) compared with background in untreated cells). In addition, after 3 hours of treatment, there were significantly more AuNPs delivered by C225 than unconjugated AuNPs (untargeted) in vitro (2.1 pg/cell \( \pm 0.1 \) pg/cell vs. 0.2 pg/cell \( \pm 0.1 \) pg/cell, respectively; \( P = 0.005 \)).

**Apoptosis-mediated cell death after C225-AuNP treatment and RF exposure in vitro**

C225-AuNPs (Fig. 4A) induced significant cell death via apoptosis 36 hours after RF field exposure, based on flow cytometric analysis (\( P = 0.00005 \) compared with untreated controls; Fig. 4B). Neither C225 treatment alone (no AuNPs) with RF exposure nor C225-AuNP treatment alone without RF induced as much cell death as the combined treatment (Fig. 4B).

**Destruction of Panc-1 xenografts due to C225-AuNP treatments and RF exposure without injury to other organs**

Excess electrical current on the surface of mice was grounded with copper conducting tape attached to the extremities in order to prevent nonspecific electrothermal injuries (Fig. 5A). Although no mice developed electrothermal injuries during RF field treatment, AuNPs in adjacent quartz cuvettes continued to heat rapidly, demonstrating the RF-induced thermal effect (Fig. 5B; Supplementary Fig. S1). Tumor temperatures in bulk rose above body temperatures by approximately 3°C during
the first minute of RF exposure and remained stable thereafter (Fig. 5B; Supplementary Fig. S1).

Despite C225 conjugation, the biodistribution of AuNPs demonstrated increased concentration in the liver and spleen, based on ICP analysis. Delivery of the C225-AuNP construct by intraperitoneal injection yielded tissue gold levels of $25.1 \pm 6.4$ mg of AuNP/g of tumor, $257.6 \pm 7.5$ mg of AuNP/g of spleen, $302.7 \pm 82.3$ mg of AuNP/g of liver, $4.0 \pm 0.3$ mg of AuNP/g of lung, and $4.1 \pm 0.1$ mg of AuNP/g of kidney. No murine tissues (liver, spleen, kidneys, and lung), demonstrated any evidence of acute or chronic injury based on histopathologic analysis despite the presence of AuNPs.

Although Panc-1 control tumors had baseline evidence of central necrosis consistent with an aggressive carcinoma, the tumors from mice treated with C225-AuNP + RF field exposure showed at least 1-grade increase in necrosis not seen in tumors from the other control groups (Fig. 6A). Panc-1 tumors exposed to RF fields after C225-AuNP treatment were significantly smaller after 6 weeks than tumors treated with C225-AuNP alone ($P = 0.0097$; Fig. 6B). In addition, cleaved caspase-3 was increased in Panc-1 tumors from mice treated with C225-AuNPs and exposed to the RF field compared with tumors from control mice (Fig. 6C and D). Tumor control was demonstrated after the first week

Fig. 2. C225 seems to quickly and uniformly bind to the surface of Panc-1 cells after treatment (durations listed at the top of each column), whereas C225-AuNP binds more slowly and in discrete, punctate morphology consistent with an antibody conjugated to AuNPs. Blue: DAPI bound to DNA; Green: AF 488-labeled secondary antibody against human IgG.

Fig. 3. AF 647–labeled C225 demonstrates significant colocalization with the secondary anti-IgG, suggesting that the C225-AuNP construct remains intact after internalization into the cell (A). Although there is mild autofluorescence (<2%) in the far red channel (second column from left, confocal microscopy), using a fluorescent threshold of 7 arbitrary units (a.u.) shows that more than 78% of cells contain measurable levels of AF 647–labeled C225 regardless if AuNPs are conjugated. B. Based on fluorescence cell counting, the percentages represent the proportion of cells with fluorescence greater than 7 a.u. whereas the $P$ value compares the mean fluorescence intensity of each distribution to the negative control.
of treatment (treatment began between weeks 1 and 2, overall \( P = 0.004 \); Fig. 6E).

The mice exposed to RF fields (with or without C225-AuNP treatment) did not show any evidence of behavior changes, gross injuries, or other signs of treatment toxicity during the experiment. Importantly, sections of the lungs, spleen, kidneys, and liver did not show any evidence of acute or chronic injury on extensive histopathologic examination despite the presence of AuNPs and RF field exposure (Fig. 6; Supplementary Fig. S2).

**Destruction of Capan-1 human pancreatic xenografts after PAM4-AuNP treatment and RF field exposure**

After demonstrating that C225-AuNP could effectively control pancreatic xenografts, we investigated this model further by utilizing a potentially more pancreatic cancer–specific antibody, PAM4, and a unconjugated AuNP + RF control arm (Fig. 6F). Capan-1 xenografts demonstrated statistically smaller tumors over the course of the experiment after PAM4-AuNP treatment, and RF field exposure began between weeks 1 and 2 (\( P = 0.035 \); Fig. 6F). Interestingly, the unconjugated AuNP + RF control arm (Fig. 6F, blue line) demonstrated early effectiveness at decreasing tumor volumes, which was lost by week 5. However, PAM4-AuNP treatment without RF exposure did not significantly reduce the size of Capan-1 tumors from the untreated controls (Fig. 6).

Similar to Panc-1 cancers, Capan-1 tumors treated with PAM4-conjugated AuNPs followed by RF field exposure were necrotic compared with control tumors treated...
with RF field exposure or PAM 4-targeted AuNPs alone (data not shown).

Again there was no evidence of injury to any of the selected organs (liver, spleen, kidneys, or lung) on histopathologic analysis in the experimental groups. Furthermore, there were no changes to gross behaviors or habits of the animals throughout the course of the experiment.

Discussion

The obvious goal, and major hurdle, of cancer therapy is to kill cancer cells without injury to normal or bystander cells, tissues, or organs. We have shown that RF fields can induce intracellular hyperthermic cytotoxicity with targeted AuNPs while controlling relatively large pancreatic cancer xenografts. Importantly, this occurred without any evidence of injury to selected normal tissues (liver, spleen, lung, and kidney), changes in animal behavior, or unexplained animal death. It is imperative that the AuNP and antibody remain conjugated until intracellular delivery. We are very confident that our constructs remain conjugated until delivery because of the optical absorption after sodium chloride challenge (Fig. 1), the diameters of the final constructs, and differences in immunofluorescence imaging.

RF field exposure in this situation was “whole-body” exposure. A consequence of this exposure is that the certain portions of animals within the field are at different electrical potentials. Variations in electrical potentials results in electrical currents that can produce a skin burn. Larger animals, however, have the body mass to absorb this “excess” current, whereas smaller animals (e.g., rodents) may have regions of increased electrical current with subsequent thermal injury to the ears, paws, and tails. To prevent this, we electrically grounded the animals’ extremities to the grounded plate of the RF device in a similar fashion to grounding pads used clinically for surgical electrocautery. Fortunately, we found this to be very effective without decreasing the ability to destroy the tumor, as the tumors were not directly isolated from the RF field. The bulk temperature of the tumors continued to rise (Supplementary Fig. S1) above the body surface temperature, consistent with bulk thermal transfer from intracellular AuNPs to cancer cells to surrounding tissues, which was visualized by the IR camera.

The in vitro experiments described herein were planned and carried out with the restrictions of the in vivo experiment in place. For example, raising the animal body temperatures above 41.5°C was presumed to be injurious to normal tissues. Therefore, the in vitro protocol was used with
these limitations. Likewise, we investigated early apoptosis at a single time point. Previous studies have shown both apoptosis and necrosis at varying time points after RF field exposure depending on the construct involved and the RF field utilized (7, 8, 22). Finally, AuNPs of slightly different sizes were used to show the effect while keeping the final construct size similar.

Although C225 was predominately utilized in this series of experiments because of ease of conjugation, it may have increased amounts of adverse events due to high expression of EGFR on the skin and in bowel mucosa among other normal tissues (23, 24). C225-conjugated AuNPs were more effective than PAM4-conjugated AuNPs in destroying targeted tumors, but C225 as a targeting agent may have more adverse clinical events because of enhanced AuNP uptake in nonmalignant tissues. PAM4 seems to be much more pancreatic cancer specific and functions only as a pancreatic adenocarcinoma targeting antibody with no intrinsic cytotoxic or growth inhibition characteristic (18, 25, 26). Furthermore, even antibodies that fail as monotherapy for pancreatic cancer may function as an effective tool to deliver AuNPs. We did not include C225- or PAM4-only control groups in our animal studies because PAM4 does not affect cell proliferation and C225 alone has not been active against pancreatic cancer cells in the current in vivo studies or previous in vitro work (8, 25). Realistically, conjugating AuNPs to several different targeting molecules that attach to ligands differentially expressed in heterogeneous cancer cell populations will be a better approach; we are currently performing such studies in vitro and in vivo. Enhancing thermal sensitivity of cancer cells may be achieved by incorporating a third component, such as a toxin or a cytotoxic drug, to the antibody-AuNP construct in order to potentiate the hyperthermic effect and impede cell repair mechanisms. In this case, the AuNP would act as scaffolding for 1 or more targeting proteins, therapeutic toxins, or chemotherapeutics to potentiate thermal toxicity, and it would also be the agent to produce heat from RF field exposure.

An obvious challenge in utilizing this therapy is the specificity of the targeting antibody as well as the nonspecific internalization by the liver and the spleen. We demonstrated that neither the lungs nor the kidneys internalized significant amounts of AuNPs. We theorize that because the kidney and lungs act as “filtering” organs in addition to their primary functions, the small size of the AuNP constructs utilized herein permit passage of these nanoparticles without accumulation, although the development of liver toxicity will need to be closely monitored in the future. However, as we have demonstrated here, there was no evidence of liver injury despite clear presence of AuNPs and RF field exposure. We suggest that the regenerative characteristics of the normal hepatocytes tolerate hyperthermic treatment more so than other tissues, including tumors (27, 28). Furthermore, there is evidence that the majority of splenic and hepatic uptake of nanoparticles is by tissue macrophages without major induction of proinflammatory cytokines (29–31). Splenic macrophages or hepatic Kupffer cells that endocytose AuNPs may be affected by RF field treatments, but these cells are rapidly repopulated from circulating macrophage populations (32). Finally, there was no evidence of acute or chronic injury, as the bulk temperatures in the liver likely remained relatively normal.

Future experiments with this modality include the development of an orthotopic model as well as the investigations of micrometastatic disease. We have demonstrated that antibody-delivered AuNPs induce significant tumor destruction in a murine model of pancreatic carcinoma after RF field exposure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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