IL-13-PE and Gemcitabine Combination Therapy for Pancreatic Cancer

Pancreatic cancer is aggressive, usually carries a poor prognosis and the standard chemotherapy regimen (gemcitabine monotherapy) has not changed in over 20 years. Although numerous phase III trials have evaluated new treatment options, none have significantly improved overall survival. Recent studies have shown a need for more effective, less toxic new treatments. Fujisawa et al. identified IL-13Rα2, a high-affinity receptor of the IL-13 cytokine family. Expression of the IL-13 receptor is increased in many human cancers, including 71% of pancreatic ductal adenocarcinomas (PDAC). To target IL-13-PE alone and combined with gemcitabine. In a pancreatic cancer model with treatment initiated on day 0, an IL-13-PE bolus injection at a suboptimal dose of 100 μg/kg/day (or 25 μg/kg/day for 14 days) and a cancer model using MIA-PaCa2 cells, which express lower levels of IL-13Rα2 compared to H1497 cells. In all cancer models, ALZET pump-infused IL-13-PE combined with gemcitabine was more effective at reducing tumors. Combination therapy was also induced greater and inhibited cell proliferation in pancreatic cancer models. Fujisawa et al. demonstrated that IL-13-PE demonstrated a therapeutic effect in pancreatic cancer model using MIA-PaCa2 and HS766T cells. Reprinted with permission from Fujisawa et al. Int. J. Cancer 2011;128:1221–1231.

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Peptides have shown promise as anti-cancer agents and could significantly enhance therapeutic performance. Anti-cancer peptides are typically designed to be small, yet potent molecules, and are particularly advantageous for use in vivo due to their ability to selectively target cancer cells. They have been shown to arrest tumor growth and to induce tumor regression in several preclinical studies.

For example, researchers at the University of Texas Southwest Medical Center are using ALZET pumps to investigate the potential use of a peptide as an anti-cancer therapy. Their strategy is to develop small, highly potent peptide ligands against vascular endothelial growth factor receptor 3 (VEGFR3), the dominant angiogenic signaling receptor, to delay growth and reduce tumor growth.

One potential benefit of these approaches is their ability to deliver a continuous and sustained drug effect, which can be particularly advantageous in cancer therapy. These peptides can be designed to have long half-lives in vivo, allowing for prolonged maintenance of therapeutic levels.

Additionally, the use of ALZET pumps enables researchers to study the antiproliferative effects of these peptides in vivo, providing valuable insights into their efficacy and potential applications in cancer treatment. These pumps are self-contained and can be implanted directly into the tumor site, facilitating steady-state delivery of the peptide and enabling accurate measurement of drug concentrations.

In summary, the use of anti-cancer peptides and ALZET pumps represents a promising approach for cancer therapy, offering the potential for effective, selective, and durable treatment of tumors.
IL-13-PE and Gemcitabine Combination Therapy for Pancreatic Cancer

Pancreatic cancer is aggressive, usually carries a poor prognosis and the standard chemotherapy regimen (gemcitabine monotherapy) has not changed in over a decade. Although numerous phase III trials have evaluated new treatment options, none have significantly improved survival. It is a desperately needed, which led researchers at the US Food and Drug Administration and Washington University to develop a novel approach by combining standard therapy with tumor-specific immunotherapy to tumor cell surface receptors. Fujisawa researchers at the US Food and Drug Administration and Washington University. They developed a recombinant immunotoxin, named IL-13-PE, by developing a recombinant immunotoxin, named IL-13-PE, by fusing the IL-13 gene to a Pseudomonas exotoxin A (PE) and injecting this immunotoxin into mice to show antitumor activity. In vitro assays demonstrated that IL-13-PE alone and combined with gemcitabine induced a potent and dose-dependent cytotoxic response against pancreatic tumor cell lines. With these encouraging results, Fujisawa then evaluated the efficacy of IL-13-PE and gemcitabine in various mouse models of human pancreatic cancer.

In all studies demonstrated that IL-13-PE alone and combined with gemcitabine induced a potent and dose-dependent cytotoxic response against pancreatic tumor cell lines. With these encouraging results, Fujisawa then evaluated the efficacy of IL-13-PE and gemcitabine in various mouse models of human pancreatic cancer.

Since 1977, ALZET® Osmotic Pumps have been used in cancer studies for continuous delivery of experimental agents to lab animals. They maximize compound efficacy with the least burden of adverse effects. For some agents, continuous dosing is more efficacious compared to administration by immediate release methods, such as injections.

In vitro, IL-13-PE was found to increase IL-13Rα2 expression in pancreatic cancer cells, explaining the enhanced therapeutic effect of IL-13-PE when combined with gemcitabine. Fujisawa et al. demonstrated that IL-13-PE and gemcitabine had synergistic activity to achieve greater therapeutic effect in vivo. Since IL-13-PE infusion was associated with increased survival, with combination therapy being most effective. In the early pancreatic cancer model, combination therapy with IL-13-PE and gemcitabine alone was the only treatment that resulted in complete excision of established pancreatic tumors. Mice treated with IL-13-PE alone or gemcitabine and continuous IL-13-PE infusion also survived without tumor recurrence. A significant therapeutic effect was also observed in the gemcitabine + IL-13-PE bolus treatment group. Notably, 4/7 mice from the gemcitabine + IL-13-PE bolus group were tumor-free on day 21, compared to 4/7 mice from the no treatment and gemcitabine group. A significant therapeutic effect was also observed in the gemcitabine + IL-13-PE bolus treatment group. Notably, 4/7 mice from the gemcitabine + IL-13-PE bolus group were tumor-free on day 21, compared to 4/7 mice from the no treatment and gemcitabine group.

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Peptoids have shown promise as anti-cancer agents and could represent a future paradigm for therapeutic peptide delivery. While monoclonal antibodies have demonstrated clinical efficacy, they are suboptimally effective and expensive and are associated with treatment-related toxicities and morbidity.

Researchers believe that peptoids are oligo-N-substituted glycines that are notably easier to synthesize but far easier to synthesize. Compared to antibodies and peptides, display enhanced serum stability and cellular permeability. In animal studies, peptoids were well tolerated. With a proven track record delivering anti-cancer agents and other therapeutic peptides, ALZET pumps are well suited for studies designed to evaluate in vivo efficacy of novel peptide therapeutics.

Researchers at the University of Texas Southwestern Medical Center are using ALZET pumps to investigate the potential use of peptoids as cancer therapeutics. Their strategy is to develop high potency peptide ligands against vascular endothelial growth factor receptor-2 (VEGFR2), the dominant angiogenic signaling receptor, to dry-staged development and retard tumor growth. After screening thousands of peptide libraries, the GU40C4 derivative was felt to be an ideal candidate for an anti-angiogenic therapy.

Once GU40C4 was shown to have strong binding affinity to VEGFR2 in vitro, the investigators proceeded to evaluate its therapeutic potential in a murine angiogenesis model. Although nude mice were injected with 9L gliosarcoma (glioma) cells, a high burden of tumor growth was observed, albeit without impacting survival. To evaluate the anti-tumor activity of GU40C4, the investigators administered GU40C4 at 1.9 mg/kg/day, same day. ALZET pumps were used to deliver GU40C4 continuously.

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Early findings showed that the GU40C4 peptide alone, which identifies the minimum pharmacophore necessary for GU40C4 recognition, is toxic in vivo studies. The development of GU40C4 derivative with reduced side effects, and "continuous GU40C4 infusion resulted in a potent therapeutic phenotype, significantly reducing tumor growth rate and volume."

Limited binding affinity in vivo studies validated the functional activity of GU40C4 wherein it was shown to share the same VEGFR2 binding site, but had superior potency over the parent compound, with a binding affinity of 12 nM (3-fold higher than Gu40C4). These studies are currently underway to further understand these variables and optimize GU40C4 peptide therapy.

In general, these studies provide insights into the therapeutic potential of peptoid-based peptide therapeutics. ALZET pumps may prove as valuable in these studies as they are utilized in studies aimed at optimizing and evaluating the therapeutic efficacy of existing chemotherapeutics in new and novel settings. ALZET pumps have been used in numerous experimental and preclinical settings, and continuous delivery of GU40C4 was shown to reduce tumor burden, significantly reduced tumor growth rate and volume, and reduced intratumoral blood flow, and a lower tumor growth index compared to controls in the absence of other treatments.

In addition, a distinct animal study was performed to determine if chronic delivery of GU40C4 was able to improve the efficacy of other chemotherapeutics. To this end, B28C12 mouse bearing 9L tumors were treated with GU40C4 (200 µg/day) and a combination of GU40C4 and doxorubicin (1 mg/kg/day) one and three times per week for 2 weeks. No adverse effects were observed. Following therapy, tumors were excised and histological sections were prepared. GU40C4 and doxorubicin were able to significantly reduce tumor size, and vessel density in a statistically significant manner. Importantly, the combination of GU40C4 and doxorubicin was able to reduce tumor size by 70% and vessel density by 30% compared to controls, confirming the anti-angiogenic effects of GU40C4. These effects were maintained one and three weeks post-treatment.

The investigators attribute these results to the fact that GU40C4 was shown to have strong binding affinity to VEGFR2 in vitro, demonstrated as a small gap between the tumor and control, and led to significantly reduced tumor burden following treatment. The investigators attribute these in vivo observations to the therapeutic potential of GU40C4, which is capable of reducing tumor burden, significantly reducing tumor growth rate and volume, and reducing intratumoral blood flow, and a lower tumor growth index compared to controls in the absence of other treatments.

In vivo angiogenic models are invaluable in studies designed to evaluate the therapeutic potential of novel anti-angiogenic agents. It is a powerful tool for studying angiogenesis in vivo and in vitro, having validated applications in both. In these studies, the investigators evaluated the therapeutic potential of GU40C4 in vivo, and found that GU40C4 was able to significantly reduce tumor burden, significantly reduce tumor growth rate and volume, and reduce intratumoral blood flow, and a lower tumor growth index compared to controls in the absence of other treatments.

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Peptides as Anti-Cancer Therapeutics

Peptides have shown promise as anti-cancer agents and could serve as a viable alternative to therapeutic antibodies. While monoclonal antibodies have demonstrated clinical efficiency, they are substantially difficult and expensive to manufacture in large quantities.

Researchers believe that peptides are an attractive alternative to antibodies due to their lower cost, increased oral bioavailability, and potential to be delivered systemically.

Once GU40C4 was shown to have strong binding affinity to VEGFR2 in vitro, the investigators proceeded to evaluate GU40C4’s ability to achieve anti-angiogenic activity in vivo. To test this, GU40C4 was injected into mice with established tumors. These tumors were treated over time with either GU40C4 or saline control. The researchers observed that GU40C4 treatment significantly reduced tumor growth, confirming its potential as an anti-angiogenic therapy.

In Vivo Animal Studies

To determine the therapeutic potential of GU40C4 peptoids, researchers designed an animal model using the 4T1 breast cancer model. In this model, tumors were established in mice, and GU40C4 was administered via ALZET pumps. The researchers monitored tumor development and growth suppression over time.

Results showed that GU40C4 treatment significantly reduced tumor growth, volume, and angiogenesis, confirming its potential as an anti-angiogenic therapy. Further studies are underway to determine the optimal dosing and delivery methods for GU40C4 in vivo.

In conclusion, GU40C4 has demonstrated promising anti-angiogenic activity in both vitro and vivo models. Further studies are needed to determine the optimal dosing and delivery methods for GU40C4 in vivo.

Cancer Research Applications

Peptide-based therapies offer several advantages over traditional chemotherapy and antibody-based therapies. Peptides have the potential to specifically target cancer cells, minimizing systemic toxicity and improving patient outcomes.

In summary, peptides have shown great promise as anti-cancer agents and could serve as a viable alternative to therapeutic antibodies. Further research is needed to fully understand the potential of peptides as anti-cancer therapies.
Pancreatic cancer is aggressive, usually carries a poor prognosis and the standard chemotherapy regimen (gemcitabine monotherapy) has not changed in over a decade. Although numerous phase III trials have evaluated new treatment options, none have significantly improved survival, with combination chemotherapy regimen (gemcitabine + IL-13-PE pump) or IL-13-PE bolus injections for both, combined and continuous administration of IL-13-PE with gemcitabine was most effective at reducing tumor growth but to a lesser extent (Figure 1). The antitumor effect of IL-13-PE was further evaluated in an advanced pancreatic cancer model with treatment initiated on day 29, an early pancreatic cancer model at a subclinical dose of 10-13-25 μg/kg/day for 14 days, and a cancer model using NIH-PaCa2 cells, which express lower levels of IL-13Rα2 compared to HS766T cells. In all cancer models, IL-13-PE pump infused IL-13-PE bolus combined with gemcitabine was most effective at reducing tumor growth. Combination therapy also induced apoptosis and intercalated cell proliferation in pancreatic cancer. Gemcitabine was found to increase IL-13Rα2 expression in pancreatic cancer cells, explaining the enhanced therapeutic effect of IL-13-PE when combined with gemcitabine. Cooling et al. demonstrated that IL-13-PE and gemcitabine synergistically to achieve greater therapeutic effect in various cancer models. IL-13-PE bolus was also well tolerated, with no evidence of organ-specific or other adverse effects. Furthermore, continuous administration of IL-13-PE pump induced a stronger antitumor response. In the research proposal that a similar therapeutic strategy may be beneficial for FDA treatment in humans. For more references on the use of ALZET pumps, visit ALZET Customer Service at www.alzet.com or email: alzet@durect.com. Since 1977, ALZET® Pumps have been used in cancer studies for continuous delivery of experimental agents to lab animals. They minimize compound efficacy by maintaining constant levels in plasma or tissues within their therapeutic range during the entire treatment period. Also, significant therapeutic effects can be reached with lower drug doses, minimizing drug toxicity and unwanted adverse effects. This Special Delivery issue highlights the effective use of ALZET pumps for evaluation of novel cancer treatments, such as peptidyl therapies and IL-13-PE immunotherapy combined with chemotherapy. Contact ALZET Technical Services for additional information or references on any of these applications.

IL-13-PE and Gemcitabine Combination Therapy for Pancreatic Cancer Osmotic Pumping System

Catheter Displacement in a Pancreatic Cancer Model

Pancreatic cancer model. Combination therapy with IL-13-PE and gemcitabine was the only treatment that resulted in complete eradication of established pancreatic tumors. Most mice in the IL-13-PE bolus treatment group (IL-13-PE bolus) had detectable tumors at day 21, compared with 8/12 mice in the gemcitabine + IL-13-PE bolus treatment group. Notably, all 6/6 mice from the gemcitabine + IL-13-PE pump group remained tumor-free throughout the course of the study (Figure 14). These animals also survived much longer, with a mean survival time (MST) of 360 days, compared to 156 and 274 days in the treatment and gemcitabine + IL-13-PE bolus groups, respectively. Figure 15 shows single-agent IL-13-PE pump treatment increased tumor size and increased survival, with a trend toward a decrease (Figure 15). The researchers propose that a combination of both agents. IL-13-PE alone and combined with gemcitabine induced a potent therapeutic effect in pancreatic cancer model. Tumor-bearing mice were implanted with orthotopic pancreatic tumors derived from HS766T and MIA-PaCa2 cells. Reprinted with permission from Fujisawa et al. Int. J. Cancer 2011;128:1221–1231.