alzet®
OSMOTIC PUMPS

Advancing Cancer Treatments with ALZET® Osmotic Pumps

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OVERVIEW

Most cancer drugs walk a fine line between therapeutic efficacy and toxicity, with a very narrow therapeutic index. Falling outside of this narrow window often results in drug failure due to inefficacy or adverse side effects. Periodic dosing exacerbates this challenge by producing wide swings in drug plasma and tissue concentrations, as a large bolus of drug is delivered at one time and then cleared. These large variations over time undermine drug efficacy and cause toxicity as concentrations fluctuate far above and below the therapeutic index. These issues are amplified in rodents, which clear drugs faster than humans, often resulting in under-dosing or requiring over-dosing to achieve average therapeutic levels. ALZET Osmotic Pumps eliminate these fluctuations. They enable researchers to attain precise and sustained drug concentrations for up to six weeks in mice or rats, maximizing drug efficacy and minimizing toxicity. The improved bioavailability provided by ALZET pumps is particularly essential for drugs with short half-lives. Altogether, these benefits vastly reduce dosing variability in animal studies, thereby improving the statistical significance of study results while minimizing the number of animals needed to successfully progress through pre-clinical trials.

ALZET pumps also offer the option for precise delivery into tumor tissues, including those within the central nervous system (CNS), through a catheter delivery system. While systemic dosing may not reach the intended target at high enough concentrations to be effective, via catheter, ALZET pumps guarantee therapeutic levels within the target tissues. In addition, targeted dosing eliminates exposure of healthy organs and tissues to

OVER 40 YEARS OF PRECISION DOSING

“With ALZET pumps, researchers can accelerate the progression to human clinical trials, maximizing chances of success while minimizing R&D costs.”

potentially toxic agents, thereby minimizing the chances of adverse side effects that are common reasons for drug failure.

The implanted ALZET pump is ideal for use in immunocompromised animal models of human cancers, requiring minimal animal handling and automatic dosing compared to traditional drug injections. This hands-off approach is not only convenient but also reduces laboratory costs and stress to animals by eliminating the need for repeated injections in unrestrained animals.

The research summarized in this white paper provides a number of examples of how ALZET pumps offer a superior pre-clinical drug dosing option for the delivery of a wide array of anti-cancer agents, including small molecules, immunotherapies, radiotherapies, combination treatments and novel drug entities. This white paper also explores how ALZET pumps have been used to successfully test treatments for cancer-associated syndromes and treatment-related side effects. With ALZET pumps, researchers can accelerate the progression to human clinical trials, maximizing chances of success while minimizing R&D costs.

EXAMPLES I: ALZET PUMPS USED IN DIRECT TREATMENT OF TUMORS

The scientific literature summarized in this white paper provides many examples where continuous administration has facilitated full development of drug effects, including those of proteins, peptides, and other rapidly eliminated compounds.

A. **Effectively testing novel and diverse therapeuticagents, alone and in combination**

B. **Advances in primary and metastatic brain tumor treatments with targeted delivery to the CNS**

C. **Testing agents to prevent relapse and metastasis induced by traditional cancer treatments**

[A] EFFECTIVELY TESTING NOVEL AND DIVERSE THERAPEUTIC AGENTS, ALONE AND IN COMBINATION

Improving therapeutic efficacy of recombinant immunotherapies and paclitaxel

Although recombinant immunotherapies (rITs) show great promise as anti-cancer agents, their efficacy, response rates and resistance profiles require improvement to make a significant therapeutic impact. In particular, B-cell malignancies like mantle cell lymphoma (MCL) and acute lymphoblastic leukemia (ALL) remain refractory against these treatments. rITs fall short against these diseases in part because of their short plasma half-life in mice and humans; after a bolus dose, blood levels fall quickly below therapeutic levels. For example, the MCL JeKo-1 cell line requires > 9 hours of rIT exposure for 50% of cells to die, but the serum half-life in mice is only 15 minutes.

"... response to CD22-targeting rIT improves more than 10-fold in the JeKo-1 xenograft model when I.V. bolus doses are exchanged for continuous infusion by osmotic pumps."

Excerpt from Muller F, et. al. Paclitaxel synergizes with exposure time adjusted CD22-targeting immunotoxins against B-cell malignancies. Oncotarget. 2017 May 9;8(19):30650.

Mueller et al. (2017) aimed to improve therapeutic efficacy of rITs with sustained dosing using an implanted ALZET infusion pump in a JeKo-1 xenograft mouse model of MCL. One mg/ml of the novel rIT LR in citrate buffer was delivered at 0.5 µl/h using ALZET Osmotic Pumps (Model 1007D), implanted into the peritoneal cavity. Alternatively, LR was I.V. injected as three bolus doses of 2.0 mg/kg every other day.

By achieving sustained dosing, Muller et al. were able to maintain a steady state plasma drug concentration of 45 ng/ml over an 8-day period, which exceeds the IC50 of the MCL cells. In contrast, the bolus dose of 2 mg/kg fell to inactive levels within less than 2 hours.

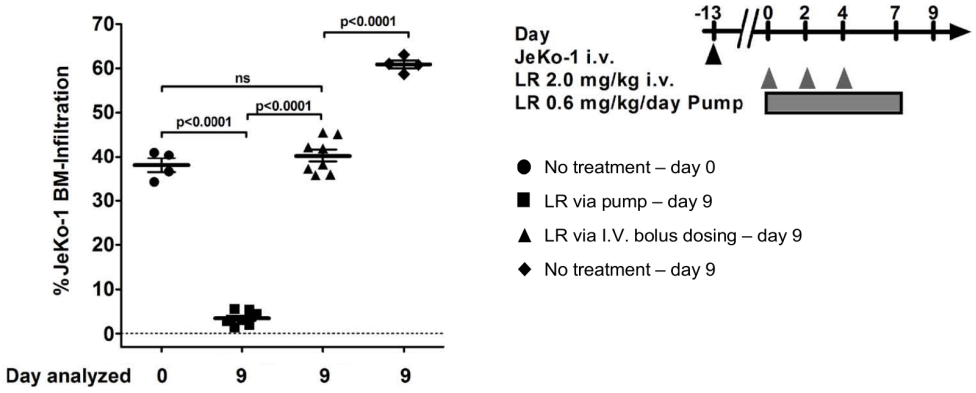
Consequently, rIT response improved more than 10-fold with the ALZET pump, reducing the JeKo-1 bone marrow infiltration rate to 3% compared with 40% from bolus dosing (three I.V. bolus doses of 2 mg/kg on days 0, 2, and 4) (Figure 1). Continuous dosing was substantially more effective even at a lower, well-tolerated total dose of 84 µg, compared to 120 µg given as three bolus doses.

"... continuous infusion and combination dosing allows for smaller overall drug doses, which are better tolerated."

Paclitaxel has been shown to enhance therapeutic efficacy of rITs in pancreatic, breast, gastric and cervical cancer models, possibly by sensitizing resistant cells to rITs. The authors also tested this combination via continuous infusion and found more than 100-fold improvement in efficacy over rIT alone, reducing bone-marrow-infiltration to only 0.1%. This high synergy *in vivo* is extremely promising for advancing to clinical trials, as similar paclitaxel/rIT combinations are already in clinical testing against other cancers.

This study highlights the importance of dosing method in attaining efficacy with rITs, underscoring continuous infusion via the ALZET pump as opposed to traditional bolus dosing to achieve and sustain therapeutic drug concentrations *in vivo*. Moreover, continuous infusion and combination dosing allows for smaller overall drug doses, which are better tolerated. These advances promise to transform the therapeutic efficacy and response rates of rITs, offering great hope to patients with B-cell malignancies that typically do not respond to these agents.

Figure 1. Bone marrow (BM) infiltration in a model of mantle cell lymphoma.



Mice received rIT LR through continuous infusion for 7 days via an ALZET pump (84 µg total dose), or via 3 I.V. bolus doses administered every other day (120 µg total dose). Compared to I.V. administration, continuous infusion of LR reduced BM infiltration by more than 10-fold.

Exploring the anti-tumorigenic effects of nitro-fatty acids

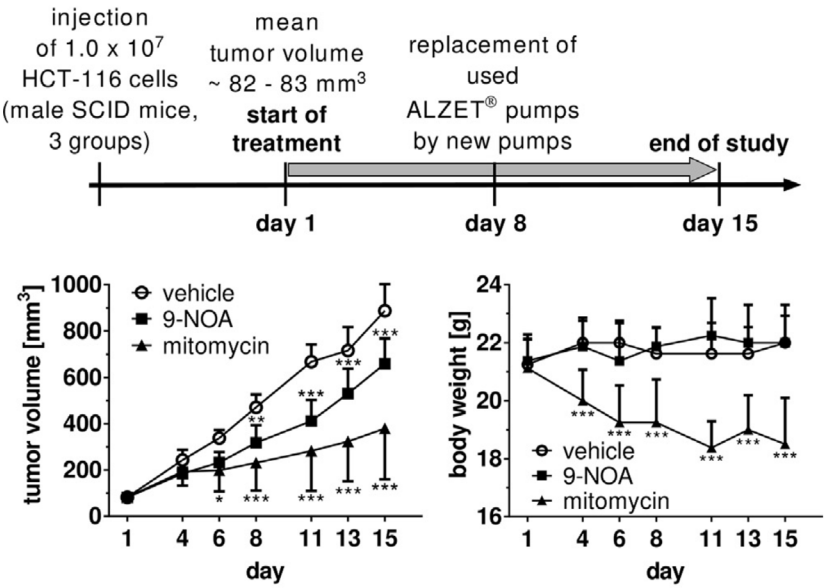
Nitro-fatty acids (NFAs) are endogenously occurring lipid mediators that exert strong anti-inflammatory and cell-protective antioxidant effects. NFAs modulate a number of intracellular targets and pathways involved in inflammation. Their suppression of various pro-inflammatory signal transduction pathways relevant to tumor growth makes them attractive anti-carcinogenic candidates.

"... we have chosen a continuous application of NFAs via ALZET® Osmotic Pumps giving the advantage of a reduction of interindividual variations in mice due to a diverse oral chow consumption behavior and therefore kept the number of animals needed as low as possible."

Excerpt from Kuhn B, et al. Anti-inflammatory nitro-fatty acids suppress tumor growth by triggering mitochondrial dysfunction and activation of the intrinsic apoptotic pathway in colorectal cancer cells. Biochem Pharmacol. 2018 Sep;155:57.

Kuhn et al. (2018) investigated the anti-tumorigenic effects of the NFA 9-nitroleate (9-NOA) in a murine xenograft model of human colorectal cancer (CRC). Vehicle and 9-NOA (16 mg/kg/day) were administered continuously via ALZET Osmotic Pump (Model 2001; 1 µl/h) rather than oral administration, giving the advantage of reducing interindividual variations in oral chow consumption and therefore minimizing animal numbers. 9-NOA treatment reduced tumor volume by 25%–30% and was well tolerated, without body weight loss (Figure 2). This is a clear advantage over traditional cytotoxic treatments like mitomycin, which have serious toxicity and safety side effects.

Figure 2. Changes in tumor volume and body weight in a colorectal cancer model.



Mice were treated with vehicle and nitro fatty acid 9-NOA (16 mg/kg/day) continuously via ALZET pump, compared to traditional cytotoxic treatment mitomycin (2 mg/kg), administered IP once every 4 days. Treatments were given for 14 days. 9-NOA reduced tumor volumes without affecting body weight.

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Kuhn et al. suggest NFAs as a new class of naturally occurring, well-tolerated chemotherapeutic drug candidates for treatment of CRC, and potentially other inflammation-driven cancers. NFAs have already successfully passed several Phase 1 studies and are entering Phase 2 trials against various inflammatory diseases, illustrating their minimal toxicity. Altogether this research identifies potential for novel alternatives to highly toxic traditional chemotherapies, which could vastly improve the quality of life and health of cancer patients.

Combination therapy to increase survival in glioblastoma

Anti-angiogenic treatments for glioblastoma like bevacizumab and other anti-VEGFR2 therapies are well-intentioned, but may ultimately induce treatment resistance and relapse with more aggressive disease. This paradoxical effect is mediated by apelin and its receptor, APLNR, which promote pro-angiogenic and invasive properties of tumor cells and vasculature by upregulation of alternative angiogenic factors.

Mastrella et al. (2019) investigate whether blocking APLNR with synthetic ligand apelin-F13A can suppress angiogenesis and invasiveness induced by anti-angiogenic therapies. In mouse models of proneural glioblastoma, apelin-F13A and anti-VEGFR2 antibody DC101 were intracerebrally infused via ALZET Osmotic Pump, alone or in combination. The pumps were attached to an ALZET Brain Infusion Kit 3, which was inserted at the site of orthotopic tumor implantation. Apelin-F13A (30 µg) was delivered in combination with DC101 (murine VEGFR2-blocking antibody corresponding to ramucirumab; 0.8 mg) over 14 days using ALZET Model 1002, or alone (60 µg) over 28 days using ALZET Model 2004.

Apelin-F13A alone rivaled the efficacy of DC101 alone, each extending survival by 19% and 28%, respectively; together, the drugs synergistically increased survival by 65%. While DC101 ultimately increased invasive tumor volume by 77%, apelin-F13A decreased this volume by 74%, while, together, the drugs reduced invasive tumor volume by 66% compared to DC101 alone.

Thus, co-administration of apelin-F13A and DC101 blunted the invasive properties of glioblastomas that are induced by traditional anti-VEGFR2 treatments. This pivotal study not only elucidates the molecular mechanism behind these adverse consequences of anti-angiogenic treatments, but also provides a novel treatment strategy to ameliorate these pathological effects by targeting the central mediator, apelin.

Sensitization of brain tumor cells to immunotoxin-based therapies

New treatments are desperately needed for both primary and metastatic brain tumors, which have dismal median survival rates (15 months for glioblastoma, 29 months for metastatic breast cancer and 25 months for metastatic melanoma). Brain tumors are particularly challenging to treat in part because they are comprised of highly heterogeneous tumor cell populations that frequently harbor inherent resistance to therapeutic agents like immunotoxins (ITs), resulting in incomplete eradication of tumor cells and tumor recurrence.

"ALZET pumps offer the tools to advance cancer drug discovery research across diverse contexts, accelerating the development of small molecules, immunotherapies, radiotherapies, combination treatments and novel drug entities from the bench to the bedside."

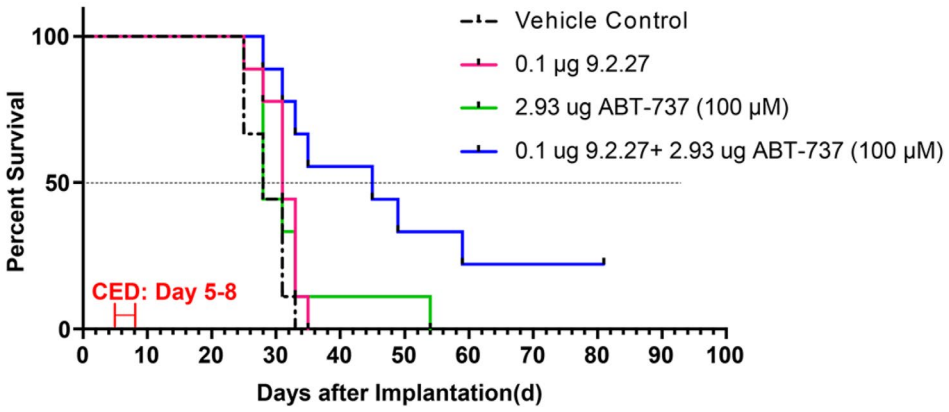
Yu et al. (2019) tested a combination drug approach to sensitize heterogenous tumor cells to immunotoxin-based therapies, utilizing pro-apoptotic enhancers to overcome IT resistance. They developed two novel immunotoxins that target the tumor cell surface marker chondroitin sulfate proteoglycan 4 (CSPG4), a biomarker of both primary glioblastomas and secondary metastatic brain tumors, as well as treatment-resistant cancer-stem cells. These ITs were paired with small molecule Bcl-2 inhibitors, which block anti-apoptotic pathways, promoting the death of cancer cells in IT studies of cervical adenocarcinoma, pancreatic cancer, and small cell lung cancer.

In primary glioblastoma and secondary metastatic melanoma brain tumor nude mouse models, a brain infusion cannula (ALZET Brain Infusion Kit 3), attached to a subcutaneously implanted ALZET pump (Model 1007D), was inserted directly into the intracranial tumor site. This resulted in intratumoral delivery of the vehicle solution or the drugs at a rate of 0.5 µl/h for 72 hours.

In both models, combination therapy significantly improved survival (61% in primary GBM model and 18% in metastatic melanoma model), while monotherapies were ineffective in all cases (Figure 3). Remarkably, in the GBM model 22% of mice treated with the drug combination were completely tumor-free at the end of the study. These cures were achieved at extremely low doses (single dose of 0.147 mg/kg of ABT-737 and 0.005 mg/kg immunotoxin) with continuous infusion directly into tumors. Meanwhile, previous studies required up to 8 doses, at 12 to 6,400 times these drug levels, to achieve only modest survival increases with no cures.

This study outlines promising new therapeutic strategies for overcoming inherent IT resistance in primary and metastatic brain tumors by sensitizing tumor cells with pro-apoptotic enhancers. ITs are already attractive drug candidates due to their excellent safety profile and potent cytotoxicity (pM-fM range), which the authors are able to maximize here by pairing their novel drug combination with the benefits of continuous and targeted delivery via ALZET pumps. With these advances, Yu et al. achieve remarkable success and even cures against aggressive brain tumors that could translate into improvements in treatments and outcomes for patients who currently have very few options.

Figure 3. Survival curves in a primary glioblastoma model.



Mice were treated with vehicle, immunotoxin 9.2.27 (0.1 µg total dose), pro-apoptotic enhancer ABT-737 (2.93 µg total dose), or 9.2.27 + ABT-737. Drugs were infused directly into the intracranial tumor site using an ALZET pump with a brain infusion kit. Combination therapy significantly improved survival while monotherapies were ineffective.

[B] ADVANCES IN PRIMARY AND METASTATIC BRAIN TUMOR TREATMENTS WITH TARGETED DELIVERY TO THE CNS

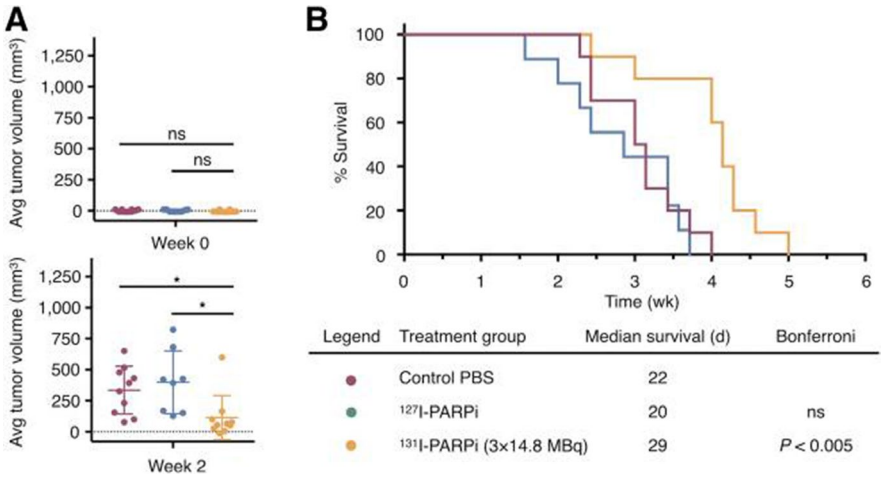
Direct infusion of chemotherapy into the brain

Breast cancer frequently metastasizes to the brain, afflicting approximately 30% of patients with secondary brain tumors. Chemotherapies that are effective against non-metastatic breast cancers, including doxorubicin, cyclophosphamide, fluorouracil, paclitaxel, and docetaxel, are ineffective against these metastases because they cannot cross the blood brain barrier. Krishnamurthy et al. (2019) tested a strategy of passive tumor targeting via hyperosmotic solution to enhance delivery of these therapeutic agents into the central nervous system (CNS) where they can combat deadly brain tumors.

"... superior method of drug administration provides accurate and sustained drug concentrations that minimize variation and error in pre-clinical animal studies"

In an immunocompromised mouse model of brain metastasis (athymic nude mice intracranially injected with MDA-MB-231 breast cancer cells), the authors infused the chemotherapeutic agent DV1 directly into the CNS using ALZET Osmotic Pumps (Model 1007D). The pumps delivered either saline or DV1 compound, at a dose of 50 µg/kg/day and dissolved in a 337 mOsm/L solution, via infusion cannula (ALZET Brain Infusion Kit 3) directly into the left brain ventricle.

Figure 4. Tumor incidence in model of intracranial metastatic breast cancer.



Saline control or chemotherapeutic DV1 (50 µg/kg/day) was administered directly into the left brain ventricle via an ALZET pump and brain infusion kit. Delivery of DV1 directly into the CNS significantly reduced the incidence of brain metastases.

OVER 40 YEARS OF PRECISION DOSING

This convection enhanced delivery (CED) method provides the advantage of increased distribution and allows a large volume of drug to be infused over time. The effective delivery of the anti-metastatic agent directly into the CNS reduced brain metastases by approximately 35%. Brain tumors developed in 83% of untreated mice, but only in 54% of treated mice (Figure 4). In addition, due to the increased vascularity of tumor tissue, the passive targeting effect of hyperosmotic solution delivered DV1 at higher levels to tumor tissues versus normal tissues.

This is an important advance on many levels. First, it suggests new therapeutic potential of DV1 against brain metastases, which currently lack adequate therapeutic options. Second, it demonstrates a new mode of drug delivery via hyper-osmotic solution that could be applied to a wide variety of cancer drugs to enhance their efficacy and improve outcomes. Third, this novel passive tumor targeting strategy might be applied against brain metastases of various origins, whether breast, melanoma, etc., or even primary brain tumors like glioblastomas, for which there are few effective or lasting treatments.

Direct administration of radiation therapy into glioblastoma cells

In a second example of direct delivery into the CNS via the ALZET Osmotic Pump, Jannetti et al. (2018) targeted radiation therapy specifically to glioblastoma cells with a novel 131I-labeled radiotherapeutic called 131I- PARPi. Radiation plays an integral role in brain tumor therapy, but also damages healthy brain tissue. The novel agent targets the DNA repair enzyme PARP-1, which is a major biomarker of glioblastomas with high expression in tumor cells but low expression in healthy brain tissue.

In two different mouse models of glioblastoma, 131I- PARPi was delivered continuously at the site of the tumor via ALZET Brain Infusion Kit 3 connected to an ALZET pump (Model 1003D). The convection-enhanced delivery method efficiently targeted and retained 131I- PARPi in orthotopic brain tumors, while quickly clearing from healthy brain tissue and non-target tissues, including liver and kidney. As a result, treated mice showed extended survival of 29 days versus 22 days for control animals.

"To mimic a potential clinical CED scenario, mice bearing orthotopic glioblastoma xenografts were treated with 131I-PARPi via implanted osmotic pumps."

Excerpt from Jannetti SA, et al. PARP-1–targeted radiotherapy in mouse models of glioblastoma. J Nucl Med. 2018 Aug;59(8):1232.

These results highlight PARP's relevance as a target for radionuclide therapy. Small molecules that target PARP are widely available, with many inhibitors currently being investigated as cancer treatments and one already FDA approved (AZD-2281). This could accelerate the development of radiolabeled PARP therapeutics like 131I- PARPi. Such targeted agents show great promise by specifically inducing DNA damage and apoptosis in cancer cells while sparing healthy brain tissue. These agents could vastly improve the standard of care for glioblastoma patients, not only extending survival but also reducing toxic side effects of un-targeted radiation treatment that impair quality of life and even induce cancer recurrence.

[C] TESTING AGENTS TO PREVENT RELAPSE AND METASTASIS INDUCED BY TRADITIONAL CANCER TREATMENTS

Blocking multiple inflammatory pathways to prevent treatment-induced relapse in ovarian cancer

Ovarian cancers have particularly poor prognoses due to the prevalence of tumor recurrence, with upwards of 70% of patients relapsing within 1-5 years of treatment. This is because front-line platinum- and taxane-based chemotherapies most commonly used to treat ovarian cancer, like paclitaxel, carboplatin and doxorubicin, actually induce tumor regrowth and metastasis. These mainstays of treatment generate tumor cell debris that triggers macrophages to release a massive "cytokine and bioactive lipid storm" of pro-inflammatory mediators, including cytokines, chemokines, prostaglandins, leukotrienes and proangiogenic growth factors. The resulting pro-inflammatory microenvironment promotes subsequent tumorigenesis, angiogenesis, and metastasis.

Gartung et al. (2019) aimed to prevent treatment-induced relapse by blocking multiple inflammatory pathways within the cytokine and bioactive lipid storm with the dual COX-2/sEH inhibitor referred to as PTUPB. This multipurpose compound suppressed both cytokine and bioactive lipid mediated inflammation in various disease models. The authors delivered PTUPB systemically at 30 mg/kg/day via ALZET Osmotic Pumps in a debris-stimulated ovarian cancer mouse model. Systemic chemotherapy with carboplatin (10 mg/kg every 3 days) or control was initiated on the day of tumor cell injection.

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The treatment effectively reduced serum levels of proinflammatory cytokines CXCL13/BCA-1 and SDF-1/CXCL12 and proangiogenic factors serpin E1/PAI-1 and IGFBP1, as well as many others. Most importantly, PTUPB treatment suppressed ovarian tumor growth and prolonged survival for over 120 days.

This study demonstrates that targeting the debris-mediated surge in pro-tumorigenic factors can be an effective strategy for enhancing the efficacy of cytotoxic therapies and preventing relapse. PTUPB provides multipurpose anti-inflammatory, anti-tumor and anti-angiogenic effects, by blocking multiple pathways within the 'cytokine and biolipid storm', thereby suppressing tumor regrowth and metastasis with minimal toxicity. As such, it is a versatile candidate for combination with traditional cytotoxic treatments, which might be applied in diverse contexts against many different types of cancers and with various therapeutic agents.

EXAMPLES II: INVESTIGATING TREATMENTS TO ALLEVIATE CANCER MORBIDITY

The scientific literature summarized below illustrates several uses for ALZET pumps in oncology research outside of tumor treatment, including accompanying syndromes and treatment-related side effects.

D. Muscle wasting (cachexia)

E. Cancer pain

F. Chemotherapy-induced hair loss

[D] MUSCLE WASTING (CACHEXIA)

Preventing cancer cachexia by blocking p300

Cancer cachexia is a muscle wasting syndrome that accounts for one-third of cancer-associated deaths. Yet there is no FDA-approved treatment for this lethal metabolic disorder, in large part because the etiology of the disease remains poorly defined. Sin et al. (2019) explored the molecular mechanisms behind the disorder in a Lewis lung carcinoma (LLC) tumor-induced cancer cachexia mouse model, discovering a major role for the p300 acetyltransferase in regulating catabolic pathway activation in muscle cells. P300 activates the transcription factor C/EBPβ by acetylating its N-terminal transactivation domain. C/EBPβ then turns on genes in the ubiquitin-proteosome pathway and authophagy-lysosomal pathway that degrade the cell.

This discovery opens the door for novel therapeutic opportunities to block the activation of C/EBPβ. By using a subcutaneously implanted ALZET pump to deliver the p300 blocking agent C646 at 10 mg/kg/day from day 7 after cancer cell injection (when the tumor became palpable), the authors were able to reduce catabolic responses, loss of muscle mass and weight loss in tumor-bearing mice, without affecting tumor growth.

While other attempts to alleviate cancer cachexia have failed in clinical trials, this study provides an understanding of pathogenic mechanisms that can be more specifically targeted to improve success. This promising advance is an important step towards broadly improving life span and quality of life for hundreds of thousands of cancer patients, across diverse cancer types.

[E] CANCER PAIN

Treating bone cancer pain by blocking pain transmission pathways in the brain

Many types of cancers, including prostate, breast and lung cancers, metastasize into bone tissues, causing excruciating pain that is inadequately managed with current analgesics. In other chronic pain conditions and neuropathies, inflammation and pro-inflammatory cytokines (PICs) released by astrocytes and microglial cells in the brain are suggested to hypersensitize pain transmission pathways in the midbrain periaqueductal

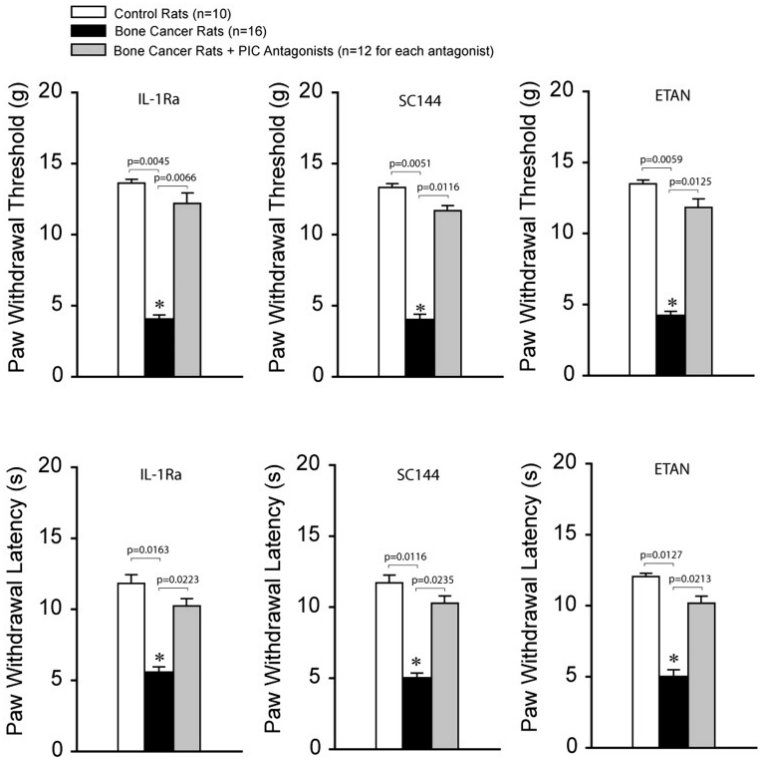
"Blocking these receptors by infusing pharmacological agents directly into these pain circuits of the brain via ALZET pumps attenuated hypersensitive responses to mechanical and thermal stimuli."

gray (PAG) region, thereby causing hyperalgesia. Zhang et al. (2019) investigated whether these inflammatory mediators contribute in the context of bone cancer pain, aiming to identify novel strategies against this distressing symptom of metastatic cancers.

The authors find that the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α and their receptors, including IL-1R, IL-6R, and TNFR1, are indeed upregulated in the dl-PAG of rats with Walker 256 breast sarcoma cells inoculated into the tibia bone cavity.

Various anti-inflammatory drugs, including rapamycin (mTOR inhibitor) and LY294002 (PI3K inhibitor) at 100 mM of concentration, and pro-inflammatory cytokine (PIC) receptor antagonists, IL-1Ra, SC144, and etanercept (ETAN), at 10 mM of concentration, were each infused directly to the dorsolateral PAG brain region using an ALZET Brain Infusion Kit connected to an ALZET pump (Model 2001D; 1 day-delivery).

Figure 5. Pain thresholds in a model of bone cancer pain.



Various pro-inflammatory cytokine (PIC) receptor blockers were infused directly into the periaqueductal gray via ALZET Osmotic Pumps and Brain Infusion Kits. PIC receptor inhibitors attenuated hypersensitive pain responses in a rat model of bone cancer.

Blocking these receptors by infusing pharmacological agents directly into these pain circuits of the brain via ALZET pumps attenuated hypersensitive responses to mechanical and thermal stimuli, as evidenced by paw withdrawal threshold and latency on a test of mechanical sensitivity (Figure 5).

This study illustrates why analgesics aimed at the periphery are inadequate against bone cancer pain, which is mediated not by peripheral physiology but by neuroinflammation of pain regulatory circuits within the brain. By specifically targeting the CNS with various anti-inflammatory agents, it is possible to correct this neuropathy and alleviate pain in mice, providing a promising strategy for treating intractable pain in patients with cancer.

[F] CHEMOTHERAPY-INDUCED HAIR LOSS

Antioxidant therapy to combat alopecia due to chemotherapy

Nearly all traditional chemotherapies cause severe hair loss known as alopecia. This common side effect of cytostatic cancer treatments like cyclophosphamide (CTX), doxorubicin, paclitaxel, etoposide, etc. is generally considered inevitable and causes significant distress to cancer patients. Lim et al. (2019) investigate the role of oxidative stress as a driver of alopecia, and the potential for the novel anti-oxidant M30 to protect against this traumatic phenomenon.

In a CTX-induced alopecia mouse model, administration of M30 at a dose of 1 mg/kg/day by subcutaneously implanted ALZET Osmotic Pump (Model 2004) improved multiple aspects of hair loss—increasing the depth and size of hair follicles and normalizing the appearance of skin and hair. These protective effects were also seen on the molecular level, via global microarray profiling—M30 treatment prevented dysregulation of hundreds of genes involved in the hair cycle phases and hair follicle development, maturation and morphogenesis.

While M30 was developed as a treatment for neurodegenerative diseases, including Alzheimer's and Parkinson's, this is the first demonstration of its protective effects against chemotherapy-induced hair loss. Not only do the authors provide a promising new treatment opportunity for this currently untreatable side effect of cancer drugs, but they also outline molecular mechanisms of alopecia pathology and M30-mediated protection to guide further research efforts towards effective clinical treatments.

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CONCLUSIONS

ALZET Osmotic Pumps have been instrumental in advancing many aspects of cancer biology and treatment by enabling researchers to study drug activities *in vivo* with great precision and ease. This superior method of drug administration provides accurate and sustained drug concentrations that minimize variation and error in pre-clinical animal studies, to accelerate the progression to clinical trials while reducing R&D costs.

With the option of systemic, tumor-targeted delivery and even intracranial infusion, ALZET pumps are applicable across diverse mouse and rat models of cancer, from blood cancers to metastatic brain tumors. Implantable infusion pumps are optimal for use in the immunocompromised animals that are commonly used in cancer studies, minimizing handling and stress to study subjects. Minimized animal handling and avoidance of repeated injection schedules that require substantial technician time also make ALZET pumps convenient and economical.

Altogether, ALZET pumps offer the tools to advance cancer drug discovery research across diverse contexts, accelerating the development of small molecules, immunotherapies, radiotherapies, combination treatments and novel drug entities from the bench to the bedside.

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DURECT Corporation
ALZET Osmotic Pumps
10260 Bubb Road
Cupertino, CA 95014-4166

Toll Free: 800-692-2990 (U.S. & Canada)

Phone: 408-367-4036

alzet@durect.com

www.alzet.com