alzet
OSMOTIC PUMPS

CANCER RESEARCH

Before a cancer therapeutic is selected for clinical development, scientists must fully characterize its mechanism of action, antitumor activity, and safety profile in preclinical animal studies. A key objective of these studies is also to optimize the schedule of drug administration in order to achieve maximum therapeutic efficacy with the least burden of adverse effects. For some cancer agents, continuous dosing is more efficacious compared to administration by immediate release methods, such as injections.

Since 1977, ALZET® Osmotic Pumps have been used in cancer studies as a dependable method for continuous delivery of experimental agents to unrestrained laboratory animals. ALZET pumps maximize efficacy by maintaining constant compound levels within their therapeutic range during prolonged treatment periods. Continuous delivery via ALZET pumps is also more efficient at reaching therapeutic effects with lower drug doses, thus minimizing drug toxicity and adverse effects. The pumps are easily connected to a catheter for delivery of agents directly into a specific target tissue, such as a tumor.

Benefits of ALZET Pumps in CANCER Research

- Small size for implantation in mice and larger lab animals
- Continuous and controlled delivery of anti-cancer agents
- Increased efficacy of therapeutic agents
- Improved bioavailability of drugs with short half-lives
- Reduced drug toxicity and side effects
- Reliable technology with over 15,000 publications
- Simple design and easy to use
- Convenient and cost-effective dosing method
- Reduced animal handling and stress
- Automatic nighttime and weekend dosing

Cancer Research Applications

Improve Efficacy and Lower Toxicity

Many chemotherapeutic agents have a relatively narrow therapeutic index, defined as a small gap between the toxic and therapeutic doses. ALZET pumps deliver at continuous and controlled rates and can maintain drug levels in plasma or tissues within their therapeutic range, enabling the effects of therapeutic compounds to develop fully and reproducibly. As a result, therapeutic efficacy can be enhanced while also minimizing adverse effects.

Use in Xenograft Models

ALZET pumps have been used in numerous *in vivo* cancer models to study the antiproliferative effects of agents and dosing schedules. Because the pumps are self-contained and require no handling during the infusion period, they are well suited for use in murine xenograft models in immunocompromised species such as SCID and nude rodents. They have been useful in the study of carcinomas of the breast, prostate, liver, skin, stomach and lung (small cell); sarcomas such as fibrosarcoma, Leydig cell, osteosarcoma; lymphomas including Burkitt's, EBV-related and EL4; and leukemias including myeloid and juvenile myelomonocytic, among others.

Intratumoral Delivery

ALZET pumps can easily be connected to a catheter to enable direct delivery of anti-cancer agents into tumors. This strategy has been shown to enhance the efficacy of some chemotherapeutics since regional tumor therapy is more efficient at reaching significant therapeutic effects with lower drug doses. Furthermore, drug levels in systemic circulation are decreased, minimizing drug exposure in sensitive organs and reducing potential side effects.

Measurement of Cell Proliferation

ALZET pumps have been used successfully to measure *in vivo* cell proliferation by continuous labeling with the base analog, 5-bromo-2'-deoxyuridine (BrdU). The pumps provide a continuous dose of the labeling agent over prolonged periods of time, which is essential for accurate measurement of slowly proliferating tissues, such as tumors. Because labeling occurs around-the-clock, results yield a true summation of the proliferative response for the entire labeling period. Continuous BrdU labeling using ALZET pumps has proven to be a more sensitive, reliable and convenient method for measuring chemically-induced cell proliferation.

In Vivo Imaging Applications

Bioluminescence imaging (BLI) is a useful experimental technique for *in vivo* imaging of small animals. It is a powerful tool for studying and monitoring ongoing biological processes (i.e., tumor growth) over time and in the same animal. ALZET pumps are increasingly being used in BLI studies as an effective means to facilitate steady-state delivery of bioluminescent substrates, such as luciferin. The pumps provide reliable and prolonged substrate delivery, thus eliminating repetitive injections and ensuring accurate detection of *in vivo* bioluminescence. ALZET pumps can be easily adapted for compatibility with BLI equipment.

Humanized Mouse Models

With the introduction of new, highly immunodeficient mouse strains (i.e., NOD/SCID, NSG), ALZET pumps are increasingly used in cancer studies with humanized mouse models. Their automatic operation, small size and simple design make them an ideal infusion system for chronic dosing studies in these species. They offer a convenient and reliable alternative to repetitive injections. No researcher intervention is required during infusion, and animal handling is kept to a minimum to reduce the risk of infection and stress.

Chronic Delivery

Chronic administration may be necessary to evaluate the long-term efficacy of anti-cancer agents *in vivo*. ALZET pumps offer a reliable and convenient alternative to frequent injections for chronic dosing of lab animals. Steady-state levels of therapeutic agents can be maintained in tissues or plasma for up to six weeks with a single pump, and the treatment duration can be extended for multiple months through serial implantation.

Selecting an Optimum Vehicle

The criteria for selecting a vehicle for ALZET pump infusion should include the solubility of the test compound, tissue compatibility, pH considerations for compound stability, and sterility. For many compounds soluble in aqueous media, Ringer's solution is an appropriate vehicle since it is sterile, particle- and pyrogen-free, and non-irritating.

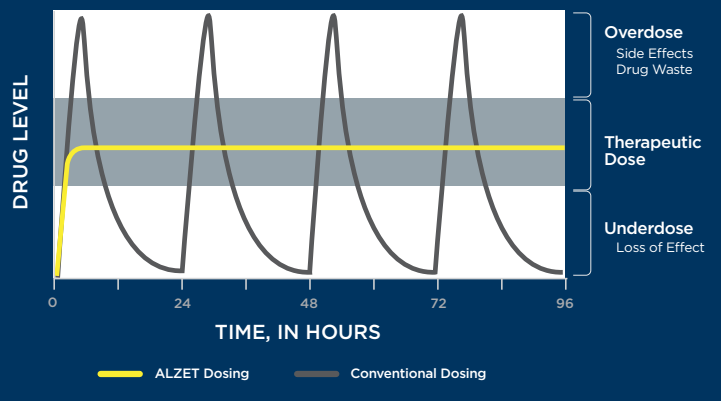
Many anti-cancer agents, especially small molecule therapeutics, are poorly soluble in aqueous vehicles due to their hydrophobic nature. For successful delivery, such compounds must be dissolved in a non-aqueous vehicle that is compatible with the pump reservoir material and effective at preventing compound precipitation during the entire dosing period. Researchers at Elan Pharmaceuticals and Pharmacyclics Inc. reported the development of a suitable solvent composition for dissolving poorly soluble compounds for preclinical studies using ALZET pumps.

Among various solvents investigated, a vehicle formulation containing **25% PEG 300, 25% Cremophor ELP, 25% glycofurol, 15% ethanol, and 10% propylene glycol** was most effective at solubilizing two investigational compounds (ELND006 and ELN 481594) with poor aqueous solubility. This formulation was fully compatible with the ALZET pump reservoir material, and the compounds remained soluble and chemically stable throughout the administration period. Furthermore, it effectively prevented compound crystallization when in contact with an aqueous environment at the site of its release, such as *in vitro* during priming of the pump or *in vivo* at the site of pump implantation.

Gullapalli et al. Drug Delivery, 2012; 19(5): 239–246

The power of continuous delivery

Injections can result in great variations in serum and tissue concentrations. Immediately after injection, compound concentrations commonly exceed effective levels, resulting in overdosing and toxicity. Rapid clearance causes periods between injections wherein the compound is absent from serum and tissues, resulting in underdosing and lack of drug effect. ALZET pumps deliver compound solutions at controlled and predictable rates, ensuring that constant and optimum levels of test agents are maintained throughout the study duration.



Cancer Research Publications

Therapeutic antibodies, MMP inhibitors, angiogenesis modulators, cytokines, siRNAs, and oligonucleotides are all examples of agents that have been successfully delivered via ALZET pumps. Below is a list of cancer agents recently added to the ALZET bibliography. Contact us to request citations specific to your research interest.

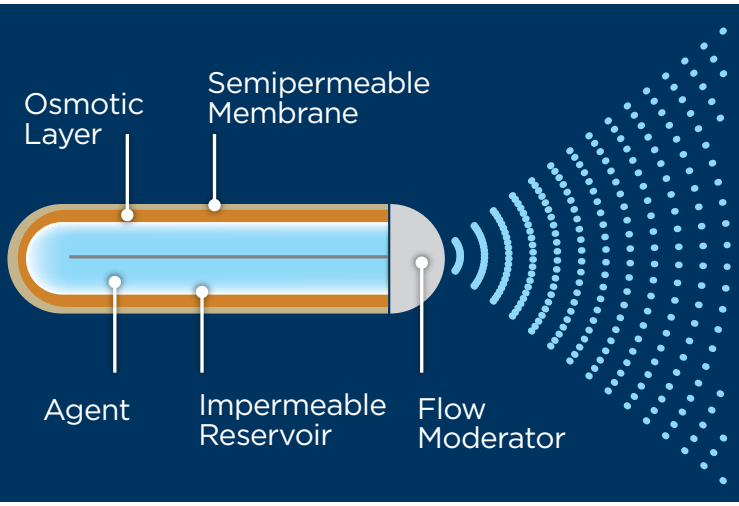
Agent	Description
F10	Fluoropyrimidine polymer
KU-60019	Ataxia–telangiectasia mutated (ATM) kinase inhibitor
gp130-Fc fusion proten	IL-6 trans-signaling blocker
5-fluorocytosine	Fluorinated pyrimidine analogue
Therapeutic stem cells	Human mesenchymal stem cells
D2C7-(scdsFv)-PE38KDEL	Anti-EGF receptor immunotoxin
Metastin peptide derivatives	KISS1R agonists
AMD3465	CXCR4 antagonist
CCX662	CXCR7 inhibitor
Alda-89	Aldehyde dehydrogenase-3 (ALDH3) activator
miR-21 inhibitor	Oligonucleotide anti-GFI1
miR-196b inhibitor	Oligonucleotide anti-GFI1
Valdecoxib	Selective COX-2 inhibitor
Parecoxib	Selective COX-2 inhibitor
DTATEGF	Diphtheria toxin
19,20-Epoxydocosapentaenoic acid	VEGF inhibitor
5-(N-ethyl-N-isopropyl)-amiloride (EIPA)	Sodium-hydrogen exchanger (NHE) inhibitor

What Leading Cancer Researchers Are Saying

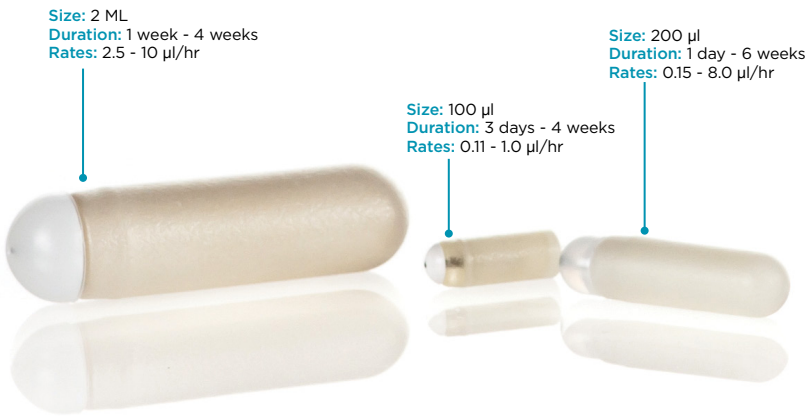
ALZET Benefit	Article Quote
Effective delivery	"...the continuous supply of therapeutic stem cells into the brain with growing glioblastoma by osmotic pumps together with continuous prodrug delivery also proved to be therapeutically efficient." *Altaner et al. Int J Cancer 2014;134(6):1458-1465*
Improve efficacy	"...we report that i.c. administration of F10 results in dramatic regression of G48a tumors." *Gmeiner et al. J Neuro-oncol 2014;116(3):447-454*
Targeted delivery	"This method of continuous intracranial delivery will aid in achieving elevated concentrations and uniform distribution of D2C7-(scdsFv)-PE38KDEL at the tumor site... to optimize its antitumor activity." *Chandramohan et al. Clin Cancer Res 2013;19(17):4717-4727*
Reduce toxicity	"...osmotic pumps... bypass the BBB/BTB and deliver drugs directly to the tumor to improve efficacy and reduce potential systemic toxicity." *Biddlestone-Thorpe et al. Clin Cancer Res 2013;19(12):3189-3200*
Reduce stress	"...we used microosmotic pumps instead of repeated injection to administer the stress hormones and antagonists to reduce the stress response as much as possible during manipulations of the animals." *Lin et al. PLoS One 2013;8(4):U1127-U1137*
Stable plasma levels	"ICG-001 was delivered via subcutaneous micro-osmotic pump to ensure stable plasma dosing levels." *Gang et al. Oncogene 2014;33:2169-2178*

How does it work?

ALZET pumps are composed of 3 concentric layers: the drug reservoir, the osmotic layer, and an outer, rate-controlling, semipermeable membrane. Once implanted, the pump begins to absorb water through the outer, semipermeable membrane. The water entering the pump hydrates and expands the osmotic layer, compressing the flexible, impermeable reservoir. As a result, test solution is released via the exit port at a controlled, predetermined rate.



ALZET Osmotic Pumps are available in 3 sizes and a range of flow rates and durations to meet your research needs



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