THE ALZET OSMOTIC PUMP NEWSLETTER – FALL 2009

Special Delivery

Volume 26, No. 1

ALZET® Osmotic Pumps are small, self-powered, infusion pumps for continuous delivery of experimental agents to laboratory animals.

ALZET pumps provide precise, continuous dosing without the need for external connections, researcher intervention or animal handling. ALZET pumps are available in various sizes. Some pump models are small enough to be implanted in mice and young rats; others are suitable for adult rats and larger animals such as rabbits, monkeys or dogs. Since their introduction in 1977, ALZET pumps have been used as a powerful, and cost-effective, experimental tool to facilitate cutting edge research. This issue of ALZET Special Delivery highlights the value of ALZET pumps in select research applications, including diabetes and obesity therapy with FGF21, siRNA therapy for neurodegenerative diseases, experimental use of novel phytochemical agents, treatment of liver injury by stem cell factor infusion, Siberian tiger conservation research and more. Please contact us if you would like further information on any research described below.

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FGF21 Infusion:
A Novel Treatment for Diabetes and Obesity

–by Jose R Gadea

While most members of the fibroblast growth factor (FGF) family are primarily involved in the regulation of cellular activities (i.e., cell division, growth and development), FGF21 has recently surfaced as a potent modulator of metabolic processes.[1,2] Studies at Lilly Research Laboratories, Division of Eli Lilly and Co., suggest that FGF21 therapy may offer a safe and efficacious option for the treatment of diabetes and obesity.

(continued on next page)

(continued from cover)

Antidiabetic Effects of FGF21

In a study published in the Journal of Clinical Investigation, Kharitonenkov *et al.* showed that therapeutic administration of FGF21 effectively lowered plasma glucose and triglycerides to nearly normal levels in diabetic mice.[1] The effects of FGF21 were initially evaluated in *ob/ob* mice, a model of hyperglycemia and insulin resistance, following once daily subcutaneous (sc) injections of 125 or 750 µg/kg/d for 7 days. Glucose-lowering effects occurred as early as 3 days into treatment with both doses; however, the FGF21 effects were more prominent after 7 days, when glucose concentrations reached normal levels in both groups. Plasma triglyceride levels were also reduced in a dose-dependent manner, with over 60% reduction at the higher dose. The researchers then evaluated the glucose-lowering effects of chronic FGF21 administration in *db/db* mice. The protein was delivered continuously for 8 weeks at an efficacious dose of 11 µg/kg/h using ALZET® Osmotic Pumps. Compared to vehicle controls, continuous FGF21 administration led to a significant and prolonged reduction in plasma glucose, as measured at days 18 and 46 of treatment. Remarkably, FGF21 treatment (even at high doses) was found to be free of the typical adverse effects associated with other therapies, such as mitogenicity, hypoglycemia, or weight gain.

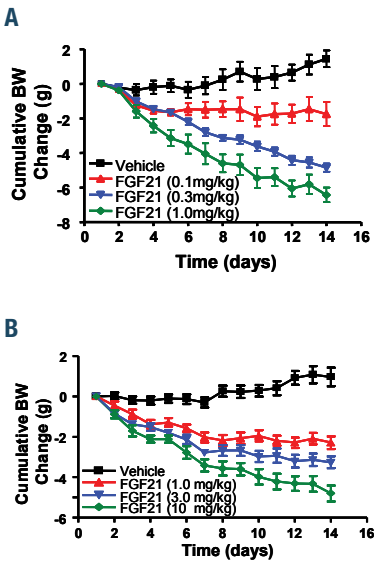


Figure 1. Cumulative change in body weights of DIO mice following continuous FGF21 administration with ALZET pumps (A), or daily bolus administration by injections (B). Note that a higher FGF21 dose is required with injections to achieve similar antiobesity effects produced following continuous infusion. [Copyright 2008. Reprinted by permission from The Endocrine Society: Coskun et al. Endocrinology 2008;149(12):6018-6027.]

Antiobesity Effects of FGF21

Having demonstrated favorable effects against diabetes, the Lilly scientists proceeded to evaluate the antiobesity potential of FGF21 in diet-induced obese (DIO) mice, a model of obesity with normal glucose and lipid levels, and *ob/ob* mice.[2] The study results, published in the Journal of Endocrinology by Coskun *et al.*, suggest that FGF21 also displays potent antiobesity effects, and that the method of administration is important in maximizing therapeutic action.

Mice were treated for 2 weeks with either vehicle, daily sc injections of FGF21 at 1.0, 3.0, and 10 mg/kg/day, or continuous infusion of FGF21 via ALZET pumps at 0.1, 0.3, and 1 mg/kg/day. Compared to vehicle controls, continuous administration of FGF21 to DIO mice led to a dose-responsive reduction in total body weight, reaching 20% with the highest dose (Fig 1A). Administration by daily injections also induced dose-dependent weight loss; however, "a 10-fold greater dose of FGF21 was required to achieve an equivalent weight reduction compared with FGF21 administration via Alzet pumps" (p. 6021)[2] (Fig 1B). Similar dose-dependent weight reduction was seen in leptin-deficient *ob/ob* mice following continuous infusion of FGF21. Coskun *et al.* attributed the antiobesity effects of FGF21 to an increase in energy consumption and fat metabolism as FGF21-treated animals exhibited increases in oxygen utilization, caloric expenditure, and core body temperature, together with a reduction in respiratory quotient. Furthermore, body and tissue composition analysis showed a significant reduction of total body fat mass, liver weight, and liver fat content following continuous administration of FGF21 in both DIO and *ob/ob* mice. Consistent with earlier studies, FGF21 administration also induced a normalization of hyperglycemia, as well as dose-dependent reductions in insulin and leptin levels.

Although both administration methods were effective at reducing weight in DIO and *ob/ob* mice, FGF21 "is significantly more efficacious when delivered via miniosmotic (Alzet) pumps" (p. 6025)[2]. Coskun *et al.* speculate that a continuous activation of FGF21 signaling is required to achieve maximal therapeutic effects. Administration via injections leads to only a temporary rise in FGF21 blood levels due to its short half-life; however, "administration via infusion allows for the continuous presence of circulating bioactive FGF21 throughout the course of the study" (p. 6025)[2]. In summary, these studies indicate that continuous administration of FGF21 offers a novel and effective strategy for long-term pharmacotherapy, with minimal adverse reactions, for the treatment of diabetes and obesity.

[1] Kharitonenkov et al. J Clin Invest. 2005;115(6):1627-1635
[2] Coskun et al. Endocrinology 2008;149(12):6018-6027

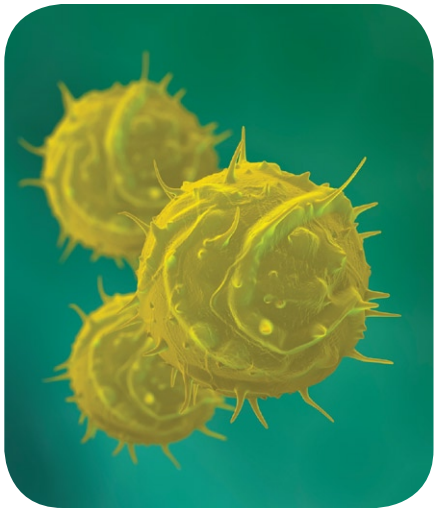
Benefits of ALZET Pumps in Research

- The only implantable pump small enough for use in mice (bigger sizes available for larger animals)
- Reliable technology – over 30 years of research
- Improved bioavailability of drugs with short half-lives
- Continuous delivery of experimental agents at controlled rates
- Increased efficacy of pharmacologic agents
- Well established research tool – over 10,500 published studies
- Simple design with no batteries or electronics to fail during the study
- Convenient & cost-effective for chronic dosing of lab animals
- Reduced toxicity and drug side effects
- Ideal for studies involving behavioral testing – no animal handling required
- Easily attached to a catheter for targeted delivery into vessels or other tissues
- Automatic nighttime and weekend dosing
- Ensures reproducible, consistent results
- Less stressful to the animal
- Saves time and money

Continuous Delivery of Stem Cell Factor Promotes Liver Recovery

–by Laura Whitman

Acetaminophen (APAP) poisoning is the most common cause of acute liver failure in the United States. Using a murine model of APAP-induced hepatic toxicity, Bin Hu and Lisa Colletti, from the University of Michigan, studied the role of Stem Cell Factor (SCF) in liver recovery. They utilized ALZET® Osmotic Pumps to administer SCF to mice with APAP-induced liver injury. "We chose the ALZET pump delivery system since we were interested in delivering continuous levels of SCF. Alternatively, SCF could have been administered one or two times a day by intraperitoneal injection; however, this method does not deliver a relatively constant level of SCF and results in peaks and troughs of this substance" (p. G46). Hu and Colletti demonstrated that exogenous SCF delivered by ALZET pumps increases hepatocyte proliferation, prevents hepatocyte apoptosis, and reduces mortality in APAP administered mice.



Liver injury was induced in wild type C57BL/6J and SCF-deficient mice by intraperitoneal (IP) injection of APAP. Exogenous SCF or PBS vehicle was administered via an IP implanted ALZET pump (Model 1003D). The pumps were filled with a 160ng/ml solution of SCF and maintained a steady state delivery for 3 days. Initial results showed that mice administered with APAP and SCF had a significantly increased survival rate compared with both SCF-deficient mice and wild-type mice given APAP alone. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured, and no differences were found between SCF-treated and control mice at any time point. This suggests that the decrease in mortality is via a mechanism unrelated to the initial hepatocyte toxicity. Thus exogenous SCF does not offer protective effects from the initial hepatic injury.

"We chose the ALZET pump delivery system since we were interested in delivering continuous levels of SCF."

Acetaminophen toxicity is often associated with hepatic centrilobular necrosis. A significant decrease in the number of apoptotic cells was seen in APAP-induced liver damaged animals treated with SCF as compared to vehicle controls. Hu and Colletti found that mice receiving APAP alone had decreased levels of the antiapoptotic Bcl-2 and Bcl-xL proteins beginning at 4 hours and reaching their lowest levels at 8 hours. Further analysis showed that this decrease was prevented by continuous SCF administration, with these mice having increased Bcl-2 and Bcl-xL expression at 8 hours. Thus hepatocyte apoptosis was suppressed in SCF treated animals, and suggesting that the decrease is mediated through Bcl-2 and Bcl-xL. Next, hepatocyte proliferation was determined by bromodeoxyuridine incorporation, which showed that continuous IP delivery of SCF significantly increased the rate of hepatocyte proliferation at 48 and 72h in APAP administered mice as compared to controls.

The use of ALZET pumps allowed the researchers to achieve constant, controlled delivery of SCF to mice with liver toxicity. Hu and Colletti were able to further stem cell research by determining that SCF enhances recovery from liver injury by increasing hepatocyte proliferation and decreasing hepatocyte apoptosis, rather than protecting directly from the injury. Lastly, these studies provide an important therapeutic indication, suggesting "that SCF may be a possible treatment for acute liver failure induced by acetaminophen or other factors" (p. G50).

Hu B, Colletti LM. Am J Physiol Gastrointest Liver Physiol 2008;295:45-53.

ALZET pumps can deliver compounds of any molecular size!

The physical or chemical properties of a compound have no influence on the delivery rate of ALZET pumps. The delivery rate of ALZET pumps is controlled by the water permeability of the outer membrane. In short, water from the environment enters the pump through the semipermeable membrane into the osmotic layer, which causes compression of the flexible, impermeable reservoir (see Figure 2, page 6). The test solution is continuously released through the flow moderator, a hollow tube with an inner diameter of 500 microns. As long as they are formulated as a homogeneous solution, even high molecular weight compounds can effectively flow through the flow moderator of ALZET pumps. Drugs of various molecular configurations, including antibodies, hormones, liposomes, or steroids can be successfully delivered at controlled rates. Contact ALZET Technical Services to request references or information on your agent of interest.

Phytochemicals as Safe Therapeutic Agents for Human Diseases

–by Jose R Gadea

Phytochemicals are plant-derived compounds which have been found to have medicinal benefits in humans. In fact, botanical agents have been used in traditional Chinese Medicine for centuries. Much of their beneficial effects are attributed to their antioxidant properties, but they have also been found to possess a wide range of other health benefits, including anti-inflammatory, antiviral, antibacterial, cellular repair, and immunity boosting activities.[1,2] Rising interest in phytochemical research has been fueled by the need for novel therapeutic agents which exhibit a lower incidence of adverse reactions during chronic therapy.[3,5,6] ALZET® Osmotic Pumps have been used successfully to deliver a variety of phytochemicals to laboratory animals, and some examples are listed in Table 1.

Table 1. Examples of various phytochemicals that have been administered via ALZET pumps

Phytochemical	Class	Sources†	Properties†‡
Ginsenosides Rb1, Rc, Rg1, Rg2, Rg3	Saponin	Panax Ginseng Root	Est, Neur, Ster
Resveratrol	Flavonoid	Tea, grapes, berries, nuts	Athe, Can, Diab, Inf, Oxi, Vira, Other
Genistein	Isoflavone	Soybeans, legumes, other	Athe, Can, Est, Oxi
Quercetin	Flavonoid	Apples, tea, onion, nuts, berries	Can, Inf, Oxi, Vira, Other
Digoxin	Glycoside	Foxglove plant	Card
Capsaicin	Phenolic acid	Chili peppers	Can, Fung
Tannic acid	Phenolic acid	Grapes, tea, nuts, pomegranate, berries, legumes, etc	Can, Oxi, Vira, Other
Soy bean peptides	Saponins	Soybeans	Diab, Obe, Oxi
Liquiritigenin	Flavanone	*Glycyrrhizae uralenses*	Est
Curcumin	Polyphenol	Turmeric root	Fung, Inf, Sep, Vira,
Caffeine	Alkaloid	Tea, coffee, chocolate	Oxi, Stim, Ure, Other

†*Properties key: Athe:Atherosclerosis protection, Can: Anticancer, Card:Cardiovascular, Diab:Antidiabetic, Est:Estrogenic, Fung:Antifungal, Inf:Anti-inflammatory, Neur:Neuroprotection, Obe:Antiobesity, Oxi:Antioxidant, Sep:Sepsis protection, Ster:steroidal, Stim:CNS stimulant, Ure:Diuretic, Vira:Antiviral*

Soybean peptides (Therapeutic indication: Obesity)

Isoflavones and high-quality dietary protein have been identified as the main contributors to the health benefits of soybeans; however, recent studies show that other soy peptides may also have positive biological effects on metabolic disorders, including obesity.[3] Jang *et al.* studied the mechanisms underlying the antiobesity effects of an isoflavone-free peptide mixture (BSP) derived from black soybean. The researchers used ALZET Osmotic Pumps (Model 1002) for continuous intraperitoneal (IP) infusion of BSP (125 µg/hr) to leptin-deficient *ob/ob* mice for two weeks. Results show that BSP significantly inhibited body weight gain and total food intake over the two week treatment period, compared to vehicle controls. In addition, a higher level of hypothalamic STAT3 phosphorylation was seen in BSP-treated mice, suggesting that the activation of leptin-like signaling is involved in the anorectic effects of BSP. Future studies will focus on the isolation and pharmacokinetics of the individual peptides responsible for these antiobesity benefits.

Curcumin (Therapeutic indication: Sepsis)

Curcumin is a phytochemical derived from turmeric (a member of the ginger family) that has anticancer and anti-inflammatory properties, and has been used safely in humans with minimal side effects.[4,5] Siddiqui *et al.* evaluated the protective effects of curcumin in an experimental model of sepsis, induced by cecal ligation and puncture (CLP).[5] Curcumin was dissolved in 50% DMSO/50% DMEM and delivered intravenously (IV) to adult rats via ALZET Osmotic Pumps (Model 2ML1). Curcumin treatment was initiated, either 3 days prior to or 5 hours after the onset of sepsis, by a single bolus dose, followed by continuous IV administration using ALZET pumps for 7 days. The researchers showed that curcumin administration, either as pre or post-therapy, offered protective effects against polymicrobial sepsis. As expected, CLP induced a 2-to-3-fold increase in serum levels of tissue injury markers (transaminases and lactate) and pro-inflammatory cytokines (TNF-α). These levels were significantly reduced with curcumin administration. The survival rate after CLP was improved to 100% in rats pretreated with curcumin, compared to 56-69% in the vehicle-treated rats. The authors further concluded that the curcumin dose regimens tested were "safe and effective in rats" (p. 1880).[5] High levels of peroxisome proliferator-activated receptor gamma (PPAR-γ) expression were also seen in curcumin-treated rats compared to controls. PPAR-γ expression was reversed following co-administration with the PPAR-γ antagonist, GW9662, via ALZET pumps. The latter findings suggest that the protective effects of curcumin in sepsis are mediated by the up-regulation of PPAR-γ leading to inhibition of proinflammatory cytokines.

Liquiritigenin (Therapeutic Indication: Menopausal Symptoms)

Currently available estrogen therapies for the treatment of menopausal symptoms are associated with an increased risk of adverse effects, including breast and uterine cancer. These effects are mediated through the activation of the estrogen receptor α (ERα), but not through ERβ activation. Researchers at the University of California, San Francisco recently identified liquiritigenin, a flavanone compound extracted from the root of *Glycyrrhizae uralenses*, as a novel ERβ agonist and safe therapeutic drug for the treatment of menopausal symptoms.[6] In a series of *in vitro* assays, Mersereau *et al.* confirmed the binding affinity and selectivity of liquiritigenin to the ERβ. Next, the researchers used a mouse xenograft model to evaluate the potential proliferative effect of breast cancer cells following liquiritigenin therapy. MCF-7 breast cancer cells were grafted under the kidney capsule of nude mice. ALZET Osmotic Pumps were used for chronic administration of liquiritigenin, estradiol (E2), or vehicle. The pumps were implanted subcutaneously, and were able "to deliver a steady dose of drug"[6] for 30 days. At the end of the treatment period, tumor xenografts and uteri were removed for size and weight measurements. Mice treated with E2 developed large tumors, while mice treated with vehicle or liquiritigenin presented no appreciable tumor growth. Furthermore, E2 treatment induced a significant increase in uterine horn mass, whereas liquiritigenin and vehicle treated mice did not display this effect. These studies suggest that liquiritigenin may provide a safer, long-term alternative for the treatment of menopausal symptoms.

[1] *Phytochemicals pages (http://www.phytochemicals.info/)*
[2] *Boyer J and Liu RH, Nutrition Journal 2004;3(5):1-15*
[3] *Jang et al. International Journal of Obesity 2008;32:1161-1170*
[4] *Jacob et al. PPAR Search 2007;2007:89369*
[5] *Siddiqui et al. Crit Care Med 2006;34(7):1874-1882*
[6] *Mersereau et al. Mol Cell Endocrinol. 2008;283(1-2):49-57*

Effective Therapeutic Gene Silencing by siRNA Infusion

–by Laura Whitman

Treatment of age-dependent neurodegenerative diseases, such as Alzheimer's, Amyotrophic Lateral Sclerosis (ALS), Huntington's, and Parkinson's, is a significant medical challenge, with high efficacy treatment lacking for all of these diseases. A promising therapeutic strategy is to inhibit the genes involved in the pathogenic pathway, which is predicted to slow disease progression and produce clinical benefit. Administration of siRNA has been shown to effectively silence specific genes, a requirement for treatment of chronic CNS diseases. However, long-term delivery of siRNA remains a critical issue. Wang *et al.* from the University of Massachusetts Medical School, successfully designed and administered a chemically stabilized siRNA against human Cu,Zn-superoxide dismutase (SOD1) using ALZET® Osmotic Pumps in a murine ALS model.

Continuous Intrathecal (IT) administration of siRNA against SOD1, mismatch siRNA or PBS vehicle to transgenic SOD1 (G93A) mice was achieved via ALZET pump Model 2004, delivering at 0.25µl/h for 4 weeks. The subcutaneously implanted pump, connected to an IT catheter, enabled targeted delivery directly into the subarachnoid space. The residual siRNA was extracted from the pump and shown to be stable after the full infusion period. Examination of various CNS regions indicated that the siRNA was able to distribute widely in the CNS following IT infusion. The researchers also confirmed that siRNA can cross the cell membrane and accumulate intracellularly, including in motor neurons. Continuous infusion of siRNA into the mouse spinal cord using ALZET pump Model 1007D, delivering 0.5µl/h for 1 week, showed a dramatic knockdown of SOD1 mRNA, confirming siRNA activity *in vivo*. To determine the therapeutic dose range, siRNA was continuously infused at 4, 8 and 16 µg/day for 4 weeks. These treatments were effective in knocking down SOD1 mRNA in a dose-dependent manner without any intolerable adverse effects. Lastly, a therapeutic trial of 4 µg/day siRNA continuous IT infusion for 28 days beginning at disease onset was conducted. The siRNA administration significantly slowed disease progression in the murine ALS model.

Wang *et al.* demonstrated that long term, IT infusion of siRNA by ALZET pumps led to widespread CNS distribution, effective cellular uptake, decreased SOD1 mRNA expression, slowed ALS disease progression and extended survival. Therapeutic gene silencing for CNS disorders has been difficult in the past due to inefficient siRNA delivery. The use of ALZET pumps allowed the researchers to achieve constant, controlled delivery of siRNA to the CNS with significant therapeutic benefit. Furthermore, "because surgical implantation of a catheter and pump is practical in humans, our study evokes a practical way for delivering RNAi therapy for CNS disorders that are incurable at present" (p. 15850). These results bring RNA interference therapy closer to a clinical application for treatment of neurodegenerative disorders.

Wang et al., Journal of Biol. Chem. 2008; 283(23):15845-15852

Release Rates and Durations

Twelve pump models available in 3 different sizes, durations ranging from 1 day to 42 days, and various release rates to meet virtually any experimental research need.

Pump Model	Reservoir Volume*	Duration	Release Rate*	Order #
1003D	100 µl	3 days	1.0 µl/hr	0000289
1007D	100 µl	1 week	0.5 µl/hr	0000290
1002	100 µl	2 weeks	0.25 µl/hr	0004317
1004	100 µl	4 weeks	0.11 µl/hr	0009922
2001D	200 µl	1 day	8.0 µl/hr	0000294
2001	200 µl	1 week	1.0 µl/hr	0000292
2002	200 µl	2 weeks	0.5 µl/hr	0000296
2004	200 µl	4 weeks	0.25 µl/hr	0000298
2006	200 µl	6 weeks	0.15 µl/hr	0007223
2ML1	2 ml	1 week	10 µl/hr	0000323
2ML2	2 ml	2 weeks	5.0 µl/hr	0000325
2ML4	2 ml	4 weeks	2.5 µl/hr	0000327

**Nominal specifications shown. Individual lots of pumps will vary from this target within acceptable limits.*

ALZET® Osmotic Pumps Aid in Siberian Tiger Conservation Research

–by Kurt Kemling

Over the last 100 years, hunting and deforestation have greatly reduced the Siberian (Amur) tiger population, whose numbers have dwindled to an estimated 400-500 in the wild.[1] Researchers at the Henry Doorly Zoo in Omaha, Nebraska are developing novel conservation programs based on artificial insemination (AI) and embryo transfer (ET) techniques in tigers in an effort to preserve their current level of genetic diversity.[2]

Ongoing studies have been designed to evaluate the tiger ovarian stimulation cycles in order to synchronize them for AI and ET. The Henry Doorly Zoo has spent several years evaluating potential recombinant hormones for use in their conservation studies. The main challenge they have encountered is that these hormones have very short half-lives, thus requiring repeated administration to sustain bioactive levels during the study period. To address this obstacle, the scientists are using ALZET® Osmotic Pumps (Model 2ML1), donated by DURECT Corporation, to reliably deliver exogenous porcine follicle stimulating hormone (pFSH) at a controlled rate over a period of 7 days. ALZET pumps enable continuous pFSH administration while eliminating the need for repeated handling and blow dart injections that are stressful to the tigers. Estrogen and progesterone levels are then assessed and compared with the natural ovarian cycle to determine the best timing for the transfer of *in-vitro* produced tiger embryos.

ALZET Osmotic Pumps have proven to be a useful delivery method for the undisturbed administration of exogenous pFSH to captive tigers, and they are playing an integral role in ensuring the future survival of the Siberian tiger species.

[1] *National Geographic pages (http://animals.nationalgeographic.com)*
[2] *Blevins, BA., Armstrong, DL., Loskutoff, NM. The Bill and Berniece Grewcock Center for Conservation & Research, Omaha's Henry Doorly Zoo, Omaha, Nebraska.*

Where is the battery?

ALZET Osmotic Pumps operate by osmotic displacement. They do not require a battery or electronics for operation. ALZET pumps are composed of 3 concentric layers: the inner drug reservoir, the osmotic layer, and an outer, rate-controlling, semipermeable membrane. The pumps operate due to an osmotic pressure difference between the osmotic layer and the environment surrounding the pump. The high osmolality of the osmotic layer causes water to enter the pump through the semipermeable membrane, which causes compression of the flexible, impermeable reservoir. This displaces test solution from the pump at a controlled, predetermined rate.

With no batteries or electronics to potentially fail, the simple design inherent in ALZET pumps gives researchers the peace of mind and extra time to focus on other important experimental variables.

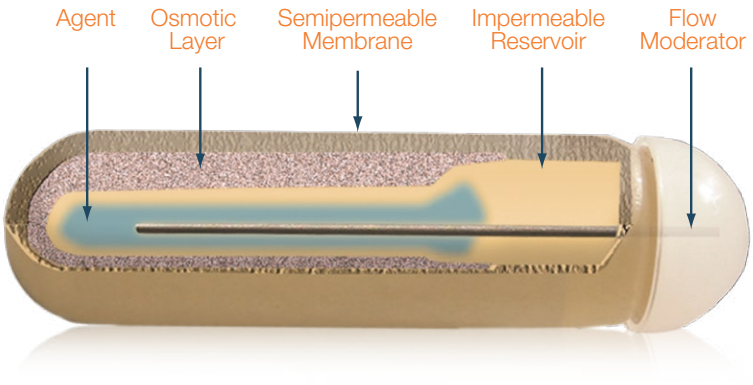


Figure 2. Cross section of an ALZET Osmotic Pump showing its design and components.

Targeted Delivery with ALZET Catheters

A range of specialized catheters, customized for a specific target and animal species, are available from DURECT Corporation to enable direct delivery of agents to a vessel, spinal cord, or other sites. These catheters incorporate useful features, such as retention beads or suture patches to facilitate placement and stabilization in a vessel or tissue. For added convenience, they are available sterile and specifically designed to attach securely to any ALZET pump model. Visit www.alzet.com for detailed catheter specifications.

CATHETER	TARGET SITE	SPECIES	CATHETER MATERIAL	CATHETER FEATURES‡	ORDER #
RJC	Jugular vein	Rat	Silicone	Dacron patch[1] Flexible material[2] Bevel tip[3]	0007710
RFC	Femoral vein	Rat	Polyurethane	Retention beads[1] Flexible material[2]	0007720
RFC-T	Femoral vein	Rat	Opaque Polyurethane	Retention beads[1] Tapered ID[4] Radio-opaque[5]	0007730
RIC	Intrathecal	Rat	Polyurethane	Occipital access Teflon coated stylet[6] Protected junctions[7]	0007740
RIC-S	Intrathecal	Rat	Polyurethane	Lumbar access Teflon coated stylet[6] Protected junctions[7]	0007741
MJC	Small vessels	Mouse	Polyurethane	Retention beads[1] 28G PU catheter tip[9] Markings on tip[8]	0007700
MJC-AL	Small vessels	Mouse	Polyurethane	Adjustable length[10] Retention beads[1] 28G PU catheter tip[9] Markings on tip[8]	0007701
MJC-LT	Jugular vein	Mouse	Polyurethane	Large tip[11] Adjustable length[10] Retention beads[1] Markings on tip[8]	0007702
Vinyl tubing	Various	Rat, mouse, other	Vinyl	Flexible material 10 per bag	0007760
PE tubing	Various	Rat, mouse, other	Polyethylene	Thermoformic 10 per bag	0007760

‡CATHETER BENEFITS

[1] Facilitates accurate placement within vessel and improves catheter patency
[2] Reduced risk of vessel trauma
[3] Facilitates insertion into vessels
[4] Tapered internal diameter (ID) for improved long-term patency and reduced risk of kinking
[5] Improved catheter patency, and reduced clotting risk
[6] Teflon coated, stainless steel stylet to facilitate insertion during cannulation
[7] Leak free catheter junctions to ensure adequate flow and minimize kinking
[8] Markings at 9 and 11 mm from tip to simplify adaptation for smaller animals
[9] Optimum for cannulating small vessels (i.e., carotid, femoral, etc)
[10] Can be trimmed to achieve smaller lengths
[11] Optimum for jugular cannulation in mice

Surgical Training Video

Learn how to use and implant ALZET pumps, or train your staff on these procedures, with the ALZET Surgical Implantation Techniques video available on CD. Request your copy today at www.alzet.com.

Coming soon... The new ALZET website!

You will find improved web page navigation, product selector and drug concentration calculators, technical tips, surgical video clips, and other downloads.

www.alzet.com

Is your vehicle compatible with ALZET pumps?

ALZET pumps are compatible with most solutions commonly used to dissolve compounds for *in vivo* administration. They are not compatible with natural oils and some organic solvents. However, low concentrations of certain organic solvents, or a mixture of solvents may be suitable for use with the pumps. The **ALZAID Chemical Compatibility Test kit** (Order #0004750) offers a simple way to determine if your dosing solution is compatible with the inner reservoir of ALZET pumps. It can be used to determine the compatibility of the solvent alone or agent-solvent combinations. The ALZAID test kit contains polymer spheres that are chemically identical to the polymer used in the reservoir of ALZET pumps. Compatibility results are obtained after simple analysis of the polymer spheres exposed to the solution in question for a specific period of time. For additional information on vehicle compatibility or the ALZAID test kit, contact ALZET Technical Support at 800.692.2990, or alzet@durect.com.

SPECIAL DELIVERY
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DURECT Corporation
Jose R Gadea, Editor

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alzet® OSMOTIC PUMPS

New Agents in the ALZET Literature

Continuous delivery via ALZET pumps allows constant levels of experimental agents to be maintained over time. The following list represents agents that have recently been delivered via ALZET pumps:

Agent	Descr./ Therapeutic Category	Ref.#
12-epi-scalaradial	*Secretory phospholipase A2 inhibitor*	P8900
17-octadecynoic acid	*CYP epoxygenase inhibitor*	P9206
BIO5192	*α4β1 integrin inhibitor*	P9168
Bone sialoproteins	*Non-collagenous, anionic phosphoproteins*	P9142
BpV(phen)	*Tyrosine phosphatase inhibitor*	P9205
BQ-610	*Type-A endothelin antagonist*	P9200
Brimonidine	*α2 Agonist, a.k.a. UK14304*	P9208
Curcumin	*Phytochemical*	P9203
Deferiprone	*Iron chelator*	P9194
DNAXTas	*Xylosyltransferase-1 deoxyribozyme*	P9079
DPI-1	*Dual phenylation inhibitor*	P9153
Eplerenone	*Aldosterone antagonist*	P8913
FTI-1, FTI-276, FTI-2148	*Farnesyl: protein transferase inhibitor*	P9153
GGTI-1	*Geranylgeranyl: protein transferase inhibitor*	P9153
GW9662	*Selective PPARγ antagonist*	P9203
IQMF-4	*Fentanyl analog*	P9157
JL 13	*Novel clozapine-like atypical antipsychotic*	P8907
Loratadine	*Tricyclic antihistamine*	P9050
Miconazole	*Antifungal agent*	P9206
MK-0731	*Kinesin spindle protein inhibitor*	P9210
MRS2578	*Selective P2Y6 receptor antagonist*	P9159
N5-2OH	*3-carboranlyalkyl thymidine analog*	P9154
Nimesulide	*COX-2 selective NSAID*	P9189
Olpadronate	*Bisphosphonate*	P9094
Oxi4503	*Vascular targeting agent*	P9204
PRAM-1	*Prorenin inhibitor*	P8979
Pyridoxal isonicotinoyl hydrazone	*Iron chelator*	P9194
Reparixin	*CXCR2 receptor inhibitor*	P8924
Rivastigmine	*Acetylcholinesterase inhibitor*	P9207
SPARC	*Angiogenesis inhibitor*	P9151
Stressin1	*Selective CRF-R1 agonist*	P9144
TAT-Bcl-XL	*TAT-fused antiapoptotic protein*	P9209
TDZD-8	*Glycogen synthase kinase-3β inhibitor*	P9006
βIIV5-3	*PKC βII inhibitor*	P9143

References on these and other agents are available to you as a complementary service. Contact ALZET Technical Services at 800.692.2990, or via e-mail at alzet@durect.com to request a customized list of references in your area of interest.