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THE **ALZET** OSMOTIC PUMP NEWSLETTER – **FALL 2007**

Special Delivery

▶ *Neuroscience Focus*

ALZET Neuroscience Research

Since their introduction in 1977, ALZET® Osmotic Pumps have always been incorporated in cutting edge neuroscience research. The ability of ALZET pumps to circumvent the blood-brain barrier (BBB) and enable direct administration of agents to the central nervous system (CNS) opened the door to new and exciting research opportunities.

This is evidenced by the pioneering works of Wei *et al.* on the study of opioid dependence in rats[1], or those of Pettigrew *et al.* studying neuronal plasticity in cats[2]. Neuroscientists quickly capitalized on the ability of ALZET pumps to provide precise, continuous dosing, without researcher intervention or animal disturbance, to use them for generating reliable data from behavioral studies, such as those involving feeding, learning, and reproduction. Three decades later, ALZET pumps continue to be an integral component in neuroscience research, as evidenced by the hundreds of publications describing the use of ALZET pumps in studies on spinal cord regeneration, neuropathic pain, stroke & ischemia, neurodegeneration, and more.

The new ALZET Special Delivery Newsletter describes select applications of ALZET pumps in neuroscience research, drawn from more than 10,000 published ALZET studies. Please contact us if you would like additional information on any of the applications described here, or if you would like to request references relevant to your research area.

[1] *Wei et al. Science 1976;193:1262-1263*
[2] *Pettigrew et al. Nature 1978;271(5647):761-763*

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CNS infusion of RNA molecules: a novel treatment for glioblastomas

–by Jose Gadea

RNA-based therapies hold great promise as potential treatment for many diseases, including glioblastoma multiforme (GBM), a highly malignant and fast growing form of brain cancer for which current therapies are ineffective.[1,2] Various experimental approaches are under investigation to evaluate and optimize RNA therapy for GBM. However, a common research challenge is that charged nucleic acids do not readily cross the blood-brain barrier.[1,2] Using ALZET Osmotic Pumps to deliver RNA molecules directly to intracranial tumors circumvents this experimental obstacle.

Researchers at the University of Illinois, led by Jasti S. Rao, are evaluating GBM therapy based on RNA interference (RNAi), in which small interfering RNA (siRNA) induce messenger RNA degradation, leading to suppression, or "silencing" of target gene expression. Their siRNA-based strategy is aimed at depriving gliomas of their means for tumor growth and invasion by suppressing expression of cathepsins, matrix metalloproteases (MMP) and/or urokinase plasminogen activator receptor (uPAR).[3,4,5] In a recent study, Lakka *et al.* evaluated the efficacy of cytomegalovirus promoter-driven siRNA vectors against uPAR and MMP-9.[3] The study showed that direct, intratumoral administration, via ALZET pumps, significantly inhibited glioma tumor growth and invasion in nude mice. Ten days after GBM tumor establishment, ALZET pumps (0.25 µl/hr)

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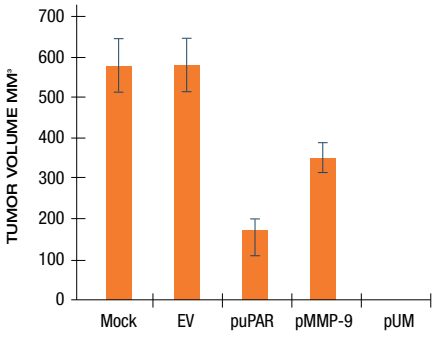
were used to directly administer the siRNA vectors into intracranial tumors via brain cannulae. After 5 weeks, tumor volume was reduced by 40 and 70% in mice treated with siRNAs for MMP-9 and uPAR, respectively, compared to controls. Complete regression of intracranial tumors was achieved in animals treated with siRNA vector for both, uPAR and MMP-9, suggesting that simultaneous blockage of uPAR and MMP-9 genes had a synergistic effect on tumor regression compared to single gene blockage *(Fig.1)*. Similar results were also observed in studies in which cathepsin B, and either MMP-9 or uPAR, were simultaneously suppressed.[4,5] SiRNA vectors were also shown to inhibit glioma cell proliferation, invasion and angiogenesis *in vitro* and *in vivo*. The scientists concluded that "local intracranial delivery of (siRNA) using mini-osmotic pumps effectively inhibited human malignant glioma growth.[6]

Other scientists at the Hebrew University of Jerusalem, headed by Alexander Levitzki, also used ALZET pumps to evaluate a novel therapeutic strategy for GBM using long, double stranded RNA (dsRNA), which have been shown to induce cell-killing mechanisms, such as apoptosis and production of anti-proliferative cytokines, in virus-infected cells.[7,8] Since GBM and other cancers over-express the epidermal growth factor receptor (EGFR), Levitzki's group investigated a ligand-directed approach to selectively target this receptor. The researchers developed a therapeutic agent composed of polyinosine-cytosine dsRNA (poly IC), a non-viral vector (PEI25-PEG-EGF) that binds to the EGFR receptor and enables entry of poly IC into the cell via endocytosis, and a polyethylenimine-Melittin (PEI2-Mel) conjugate that facilitates the release of poly IC from endosomes.[8] *In vitro* studies confirmed that poly IC induced fast and selective killing of EGFR over-expressing cells while sparing all others. *In vivo* efficacy was then assessed in nude mice by using ALZET pumps to administer either poly IC or control vector (CV) for 3-5 days directly into pre-established glioma tumors. Histological and pathological evaluation of brains from poly IC-treated mice revealed complete tumor eradication and no toxicity, confirming *in vivo* efficacy and safety of poly IC. On the other hand, large tumors reaching up to 36.44 mm^3 in volume were seen in the control groups. Survival studies showed that CV-treated and untreated mice lived for no more than 32 days; however, and most impressively, all tumor-bearing animals treated with poly IC survived for more than a year *(Fig. 2)*. Dose-escalation studies to investigate the bystander effect (killing of neighboring tumor cells) of poly IC on animal survival showed that higher doses (0.4 and 0.8 µg/hr) extended survival to over 297 days, compared to 68 days at the lowest dose (0.2 µg/hr) and 34 days in the control groups. Furthermore, dsRNA treatment was also replicated in two other EGFR over-expressing tumor models (cervical and breast carcinoma), suggesting that this approach has broad therapeutic potential.

These studies validate the use of ALZET pumps in GBM research for effective delivery of RNA molecules to the CNS. Gondi *et al.* concluded that "mini-osmotic pumps maintain a well-defined and consistent pattern of drug exposure for a significant period of time and can be used successfully to deliver agents to the brain".[9] Furthermore, Shir *et al.* reported that local therapy by slow, constant, intratumoral delivery of dsRNA complexes produced the most effective treatment of EGFR over expressing GBM reported so far in pre-clinical studies.[8] Other investigators also favor direct infusion as the best delivery option,[1,2] indicating that local delivery enables "high concentration at the intended target site while using a low dose and minimizing risk of systemic side effects".[10]

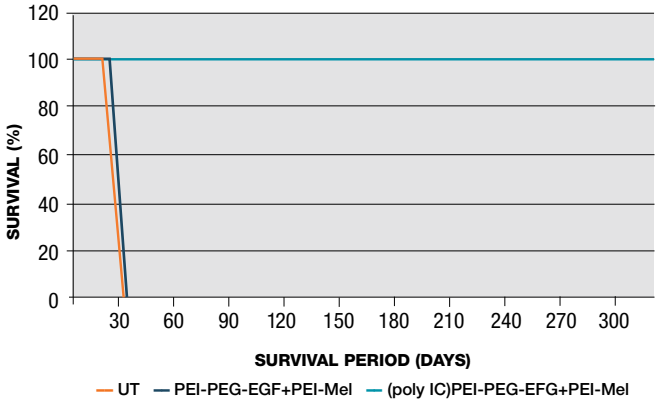
"local intracranial delivery of (siRNA) using mini-osmotic pumps effectively inhibited human malignant glioma growth"

[1] *Behlke, M. A. Molecular Ther 2006;13(4):644-670.*
[2] *Mathupala, S. P. et al. Tech Cancer Res Treat 2006; 5(3):261-269.*
[3] *Lakka, S. S. et al. J BiolChem 2005;280(22):21882-21892.*
[4] *Lakka, S. S. et al. Oncogene 2004;23:4681-4689.*
[5] *Gondi, C. S. et al. Oncogene 2004;23:8486-8496.*
[6] *Gondi (2004); pp. 8493.*
[7] *Friedrich, I. et al. Seminars Cancer Biol 2004;14:223-230.*
[8] *Shir, A. et al. PloS Medicine 2006;3(1):0125-0135.*
[9] *Gondi (2004); pp. 8493.*
[10] *Behlke (2006); pp. 649.*



(Figure 1) *RNAi-mediated regression of glioma tumor growth. Glioma tumors were allowed to grow for 10 days in nude mice. Then, ALZET pumps were used for continuous administration of mock, EV (empty vector), puPAR, pMMP-9, and pUM (plasmid siRNA vector for uPAR and MMP-9) vectors. Tumor volume was assessed 4-6 weeks after tumor cell implantation.*

Reprinted with permission from Lakka et al. J. Biochem 2005;280(22):21882-21892.



(Figure 2) *RNA infusion therapy enhances the survival of animals with glioma tumors. Intracranial tumors were established in nude mice. After 10 days, a group of animals received continuous infusion of poly IC complexes via ALZET pumps for 48 hours, another group received CV infusion (PEI-PEG-EGF+Mel), and a third group remained untreated (UT). Survival of the animals was assessed for longer than 300 days.*

Reprinted with permission from Alexander Levitzki and Shir et al. PloS Medicine 2006;3(1):0125-0135.

Effective Epileptic Treatment Requires ***Continuous Drug Delivery***

–by Laura Whitman

Alternate treatments for pharmacoresistant epilepsy are in great demand. Valproic acid (VPA) is a first-line antiepileptic drug that is highly effective. However, its hepatotoxicity limits chronic use. Serralta *et al.* used ALZET pumps to determine whether continuous intracerebroventricular (ICV) infusion of VPA could avoid systemic toxicity, achieving therapeutic drug concentrations in the brain yet low peripheral organ concentrations. Two VPA administration protocols were tested to assess anticonvulsant efficacy, hepatotoxicity and neurotoxicity.

Effective targeted delivery of VPA was accomplished using a subcutaneously implanted ALZET pump connected to a catheter and cannula placed into the lateral ventricle of amygdala-kindling epilepsy model rats. ALZET Models 2001 and 2002 were used to establish two different dose groups. Anticonvulsant effect was evaluated daily during infusion and for 5 days after pump removal. Alternatively, rats were given VPA injections (ICV or intraperitoneal (IP)) and tested for anticonvulsant effect 5-30 minutes afterwards. Animals were evaluated for generalized and focal seizure suppression, and neurological side effects. In addition, VPA levels in the brain, plasma, CSF and liver were determined.

ICV injections controlled both generalized and focal seizures, but only with considerable levels of ataxia and sedation. Drug concentrations and efficacy declined rapidly within 5-15 minutes post-injection. IP injections showed less control of seizures, required a higher dose of VPA and were also associated with high levels of ataxia and sedation. The side effects and stress of repeated injections led the researchers to conclude that this was an unacceptable method of VPA administration.

In contrast, continuous ICV administration using ALZET pumps controlled both generalized and focal seizures with low neurotoxicity, and very low plasma and hepatic concentrations. Continuous infusion led to a progressive decrease in seizure severity with increasing dosages and infusion times. By day 4, all animals receiving 0.8 mg/h VPA via ALZET pumps were seizure free. Toxicity was low to nonexistent during and after the infusion period, with no sedation in any animals and low (level 1) ataxia in only four of six high dose animals.

The use of ALZET pumps allowed the researchers to achieve constant, controlled delivery of neuroactive VPA directly to the CNS, controlling kindled seizures without the toxicity involved in systemic administration. Lastly, these studies suggest a potential clinical application for continuous ICV anticonvulsant administration in pharmacoresistant epilepsy.

Serralta et al. Epilepsy Research 2006;70:15-26

Continuous Infusion of SM-216289 Improves Regeneration of Spinal Cord After Injury

–by Kurt Kemling

Spinal cord injury (SCI) affects over 250,000 Americans, with 11,000 new injuries occurring every year[1]. A vital component in emergent recovery therapies is the understanding of axonal regeneration after injury. It has been shown that axonal regeneration is inhibited by several extracellular factors, including Semaphorin3A (Sema3A), present at the site of injury. Neutralization of Sema3A inhibitors with pharmacological agents presents a viable option for therapy. In a recent study, Kaneko *et al.* used ALZET osmotic pumps to assess the regenerative potential of SM-216289, a Sema3A inhibitor isolated from fungal extracts[2].

Kaneko *et al.* confirmed the presence of high levels of Sema3A in scar tissue, which peaked at 1-2 weeks after SCI. Using a collagen coculture assay and growth cone collapse assay, SM-216289 was shown to be a strong and selective inhibitor of Sema3A. To characterize its pharmacodynamic activity *in vivo*, SM-216289 was delivered to adult rats with spinal transection at T8 for four weeks via ALZET pump (Model 2004). Pumps were connected to a catheter leading directly to the injury site. Immunohistochemical analyses showed significantly higher levels of neurofilament-positive axons and growth-associated protein 43 (GAP43), a marker for regenerating axons, at the lesion site of SM-216289 infused animals compared to controls. These findings suggest a more vigorous axonal regeneration in SM-216289-infused animals. Furthermore, SM-216289 enhanced migration of Schwann cells to the injury site to aid in the regeneration process. Continuous delivery of SM-216289 was also shown to promote angiogenesis and inhibit neuronal apoptosis, conferring neuroprotection at the lesion site.

Researching potential therapies for post SCI recovery has been a major cornerstone in neuroscience research and is a growing application for ALZET pumps. The present study established that rats chronically treated with SM-216289 showed improved axonal regeneration, enhanced functional recovery, and neuroprotection. ALZET pumps allowed for direct delivery into the CNS and helped demonstrate the potential use of SM-216289 as a therapeutic agent for SCI patients.

[1]Spinal Cord Information Pages (http://www.sci-info-pages.com/facts.htm);
[2]Kaneko et al. Nature Medicine 2006;12:1380-1389.

Benefits of ALZET Pumps in Neuroscience Research

- The only implantable pump available for use in mice and young rats
- Continuous and controlled delivery of neuroactive compounds
- Direct delivery of agents across the blood-brain barrier
- Improved bioavailability of short half-life peptides and proteins
- Ideal for studies involving behavioral testing - no animal handling required during infusion
- Easily attached to a catheter for delivery to the brain, spinal cord, or peripheral nerves
- Convenient & cost-effective for chronic treatment in lab animals
- Over 30 years of published neuroscience research (well-established methods for many animal models)
- Automatic nighttime and weekend dosing
- Reproducible, consistent results

Why Neuroscientists Use ALZET Pumps in Their Research*

"We decided to administer it [creatine] by intracerebroventricular infusion to maximize its bioavailability to the brain."

(p. 187) Lensman et al. Brain Research 2006:187-194

"To avoid injection-induced stress and fluctuations of imipramine and the metabolite levels, we administered imipramine using osmotic minipump."

(p. 84) Fujita et al. Synapse 2007; 61:78-86

"The use of an osmotic minipump allowed a constant exposure to low doses of CPF-0, simulating continuous environmental exposure."

Laviola et al. Psychopharmacology 2006; 187:331-344

"We chose direct intratumoral delivery as route of application for the OA-5D5 antibody because antibodies are large molecules that permeate the blood-brain barrier only insufficiently."

(p. 6150) Martens et al. Clin Cancer Res 2006;12(20):6144-6152

"… olanzapine was infused subcutaneously by osmotic mini-pumps, thus avoiding the stress-associated procedures of gavage administration. Moreover, osmotic slow-release permitted to face the problem of antipsychotics dosing in animal models."

(p. 562) Coccurello et al. Psychopharmacology 2006;186:561-571

"The use of an osmotic pump permits the rat to be free from constraints of the standard tethered system."

(p. 269) Cooper et al. J Neurosci Methods 2007;160(2):269-275.

"The use of osmotic pumps may be more effective than daily injection because of the short half-life of 8-OH-DPAT."

(p. 810) Huang et al. Neuroscience 2005;135:803-813

"This long-term delivery system [ALZET pump] increases therapeutically available IGF-1 at least 30-fold as compared to single subcutaneous injections."

(p. 138) Fernandez et al. Brain Research Reviews 2005;50:134-141

*Selected quotes from recent publications

Tetherless Microdialysis Sampling Enabled by **ALZET Pumps**

–by Clarisa Peer

First described in the literature in 1974, microdialysis is a well-developed technique for monitoring the chemistry of extracellular fluid *in vivo*. When applied to the brain, it can offer insight into the intracranial dynamics in acute conditions, such as ischemic stroke and traumatic brain injury. However, current methods are cumbersome, expensive and confine tethered animals to a small container. These factors render microdialysis prohibitive for some lab budgets, and also for studies hinging on free movement of the animal, such as behavioral or exercise physiology research, or even protocols requiring special caging.

*"The new method offers significant advantages related to **cost, convenience and portability** without sacrificing performance."*

As early as 1991, researchers have used ALZET pumps in microdialysis studies, even infusing drugs through the microdialysis probe in order to improve their distribution in brain parenchyma.[1] However, a new study by Cooper *et al.* describes a method using ALZET pumps instead of syringe pumps for microdialysis sampling from awake and untethered rats. The new method offers significant advantages related to cost, convenience and portability without sacrificing performance.[2]

Having first assessed the *in vitro* performance of ALZET pumps with the microdialysis probes attached, Cooper then incorporated them into a completely

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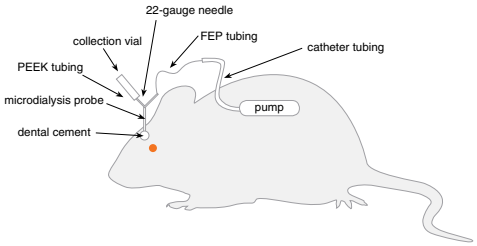

(Figure 3) *Schematic of the sample collection system with the microdialysis probe and osmotic pump.*

Reprinted with permission from Cooper et al, J Neurosci Methods 2007;160:269-275

portable, on-animal system for *in vivo* sampling of neurotransmitters. Model 2ML1 ALZET pumps (subcutaneous placement) and CMA3 brain cannulae (right striatum) were implanted in a single surgery. The ALZET pump was filled with lactated Ringer's and connected to the inlet port of a CMA/12 microdialysis probe (20,000 Da molecular weight cut-off) using FEP tubing from BAS.[4] A BAS tubing connector was used to splice the pump and FEP tubing together, and this connection was safeguarded with both UV-gluing and a generous sheath of tubing protector. A small collection vial was attached to the probe's outlet *(Fig. 3)*. Samples were collected hourly from the awake and freely moving rat by replacing the collection vial.

After 24-48 hours for recovery and baseline sampling, rats were dosed intraperitoneally with benserazide, shown to prolong elevated concentrations of neurotransmitters, and then L-DOPA. HPLC analysis of the samples demonstrated significantly increased concentrations of DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid), both in the L-DOPA metabolic pathway, for all rats, and with similar pharmacokinetic profiles.

The authors note that "one of the disadvantages of the osmotic pump approach is that it is not useful for studying very fast processes occurring *in vivo*...(However) due to the low flow rates employed, the osmotic pumps are particularly attractive for long-term studies in which the desired temporal resolution is on the order of hours or days as opposed to minutes...(and for) microdialysis experiments investigating analytes that occur at low concentrations *in vivo*."[5]

[1] *Bazzett TJ, Becker JB & Albin RL. J Neurosci Methods 1991;40:1-8.*
[2] *Cooper JD, Heppert KE, Davies MI & Lunte SM. J Neurosci Methods 2007;160:269-275.*
[3] *CMA, Stockholm, Sweden: www.microdialysis.com*
[4] *Fluorinated ethylene propylene (FEP) tubing, 0.65 mm OD x 0.12 ID, Bioanalytical Systems (BAS), www.bioanalytical.com*
[5] *Cooper (2007); pp. 273-274.*

Intracerebral Infusion in Mice

With the emergence of new transgenic, selectively bred, and knockout strains, mice are increasingly being used in neuroscience research. Similarly, ALZET pumps are a popular method for enabling delivery of neuroactive agents across the BBB, directly into a specific region of the mouse brain. The following table summarizes recent research on the use of ALZET pumps for CNS delivery of agents to mice, and describes the stereotaxic coordinates used to target a specific brain region.

TARGET	COORDINATES	AGENTS INFUSED VIA ALZET PUMP	CITATION
Lateral ventricle	0.1 mm anteroposterior to bregma; 0.9 mm lateral from midline; 2.5 mm below the dura	Ara-C, LIF, EGF	*Bauer et al. Leukemia inhibitory factor promotes neural stem cell self-renewal in the adult brain. J Neurosci 2006;26(46):12089-12099*
Ventral tegmental area	–2.9 mm anteroposterior; +1.0 mm lateral; –4.4 mm ventral medial	BIM28163	*Abizaid et al. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J Clin Invest 2006;116(12):3229-3239*
Frontal lobe (tumor)	1 mm anterior to coronal suture; 3 mm lateral from midline; 5 mm into frontal lobe	Contortrostatin	*Pyrko et al. The role of contortrostatin, a snake venom disintegrin, in the inhibition of tumor progression and prolongation of survival in a rodent glioma model. J Neurosurg 2005;103(3):526*
Lateral ventricle	0.1 mm anteroposterior; -1 mm lateral; -3 mm dorsoventral	Ganciclovir	*Simard et al. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron 2006;49(4):489-502*
Parenchyma	1 mm anterior to bregma; 2 mm lateral; 3 mm from skull surface	VEGF	*Schmidt et al. Brain tumor tropism of transplanted human neural stem cells is induced by vascular endothelial growth factor. Neoplasia 2005;7(6):623-629*
Right lateral ventricle; Third ventricle	Right lateral ventricle: 0.4 mm posterior to bregma; 0.8 mm lateral to midline; 2.0 mm from skull surface. Third ventricle: 0.22 mm posterior; 0.3 mm lateral; 3.3 mm ventral to bregma	Melanin-concentrating hormone 1 receptor antagonist	*Mashiko et al. Antiobesity effect of a melanin-concentrating hormone 1 receptor antagonist in diet-induced obese mice. Endocrinology 2005;146(7):3080-3086.*

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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.

ALZET Products for Neuroscientists

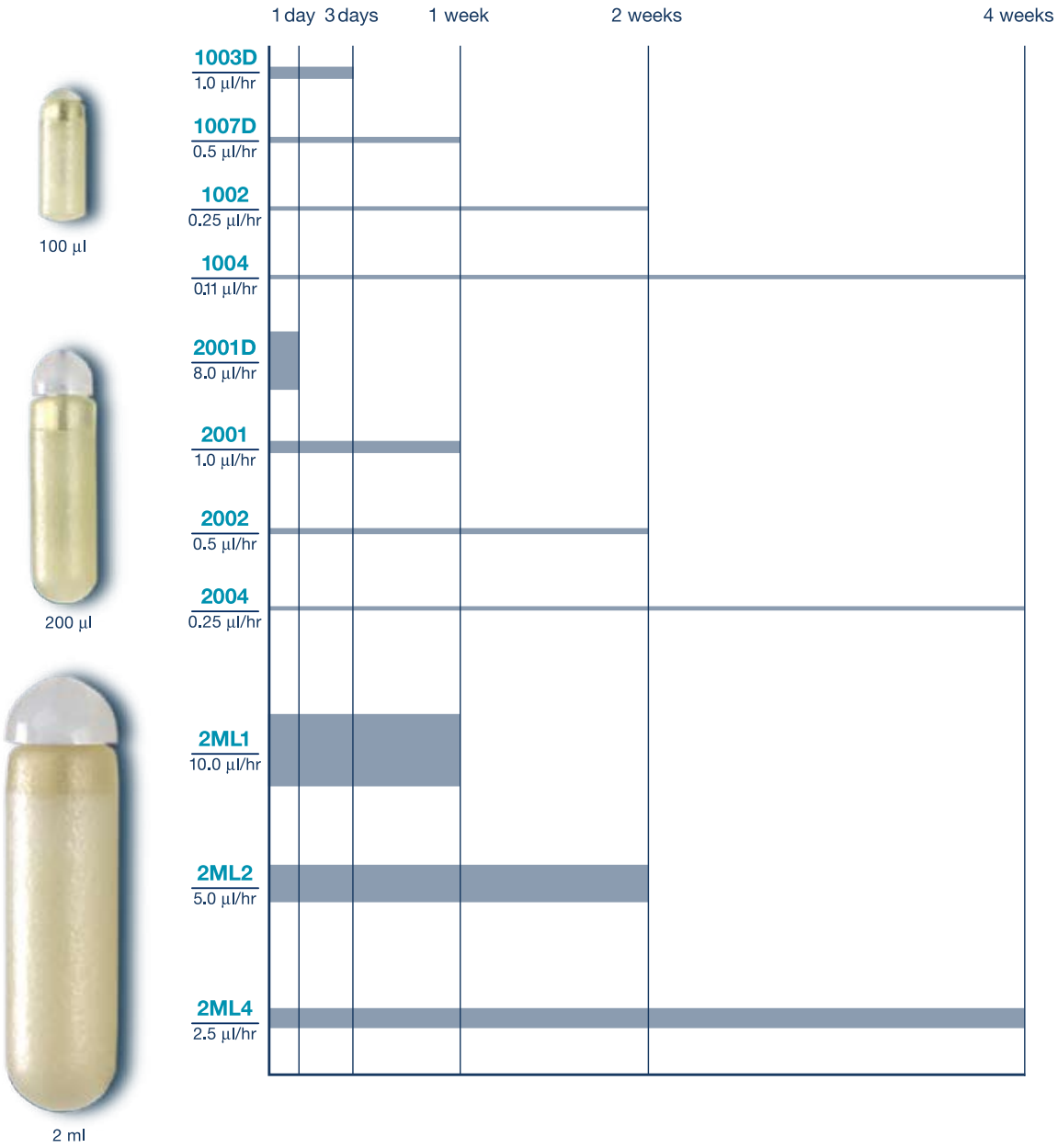
PRODUCT	ITEM #
ALZET Osmotic Pumps Eleven pump models available in 3 different sizes, durations ranging from 1 day to 28 days, and various release rates.	various
Brain Infusion Kit 1 (materials for 10 brain infusions; cannula features: 28G, 3-5 mm length)	0004760
Brain Infusion Kit 2 (materials for 10 brain infusions; cannula features: 28G, 3-5 mm length, low profile and wide pedestal)	0008663
Brain Infusion Kit 3 (materials for 10 brain infusions; cannula features: 30G, 1-3 mm length, low profile and wide pedestal)	0008851
Loctite 454 Cyanoacrylate Adhesive (instant adhesive gel for securing cannulae to the skull)	0008670
Rat Intrathecal Catheter (Polyurethane (23.7 cm total length), includes 10 cm of very fine tubing (OD 0.36 mm); teflon-coated, stainless steel stylet)	0007740
Rat Intrathecal Catheter Short Shorter length for non-occipital approach. (Polyurethane (15 cm total length), includes 10 cm of very fine tubing (OD 0.36 mm); teflon-coated, stainless steel stylet)	0007741

Neuroscience Publications

Therapeutic antibodies, enzyme inhibitors, antidepressants, anticonvulsants, dopaminergics, opioids, neuropeptides, neurotrophic factors, and nucleic acids are all examples of agents that have been successfully delivered via ALZET pumps. New publications for these and other experimental agents are constantly added to the ALZET bibliography. Contact us to request citations specific to your research interest.

ALZET Osmotic Pumps – Durations and Release Rates

Eleven pump models available in 3 different sizes, durations ranging from 1 day to 28 days, and various release rates. With this wide selection of pumps, scientists are sure to find one that meets their experimental research needs.



ALZET Catheters

Medical grade polyethylene and vinyl catheters are available for multiple targeted delivery applications. Also available are a variety of specialized catheters, customized for a specific target and animal species. 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 individually packaged. The following catheter types are available:

- Mouse and rat jugular catheters
- Rat intrathecal catheters
- Rat femoral catheters

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When designing a new study or completing a grant application, it is critical to obtain up-to-date information quickly. For technical information about ALZET pumps, visit our website at www.alzet.com. You will find easy web page navigation, a detailed "Guide to use" for ALZET pumps, and many downloadable technical resources.

Recently Infused Agents

Continuous administration is a popular modality for drug administration in neuroscience studies. The following list represents new neuroscience-related agents that have recently been delivered via ALZET pumps. 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.

Agent	Descr./ Therapeutic Category	Ref.#
TLQP-21	*VGF-derived neuropeptide*	P7973
Contortrostatin	*Snake venom disintegrin; Anticancer agent*	P7975
Artemin, recomb. human	*GDNF family factor*	P7974
S100B	*Brain-specific, Ca^{2+}-binding protein; Neurotrophic mitogen protein*	P8055
Nociceptin/orphanin FQ	*Neuropeptide (opioid, nociceptive)*	P8054
Nesfatin-1	*Neuropeptide (saciety peptide)*	P7966
GBR12783	*Selective dopamine reuptake inhibitor*	P7954
Methyllycaconitine	*Selective 7 nicotinic acetylcholine receptor antagonist (7 nAChR)*	P7893
Epopeptide AB	*Neuroprotective factor (ischemia)*	P7869
Galanin-like peptide (GALP)	*Neuropeptide; hormone regulator*	P7776
H409/22	*Neuropeptide Y-Y1 receptor antagonist*	P7490
Iberiotoxin	*Neurotoxin*	P7677
Neuroserpin	*Serine proteinase inhibitor*	P8053
4-amino-7 phenylpyrazol[3,4-d]pyrimidine (PP3)	*Tyrosine kinase inhibitor*	P8118

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