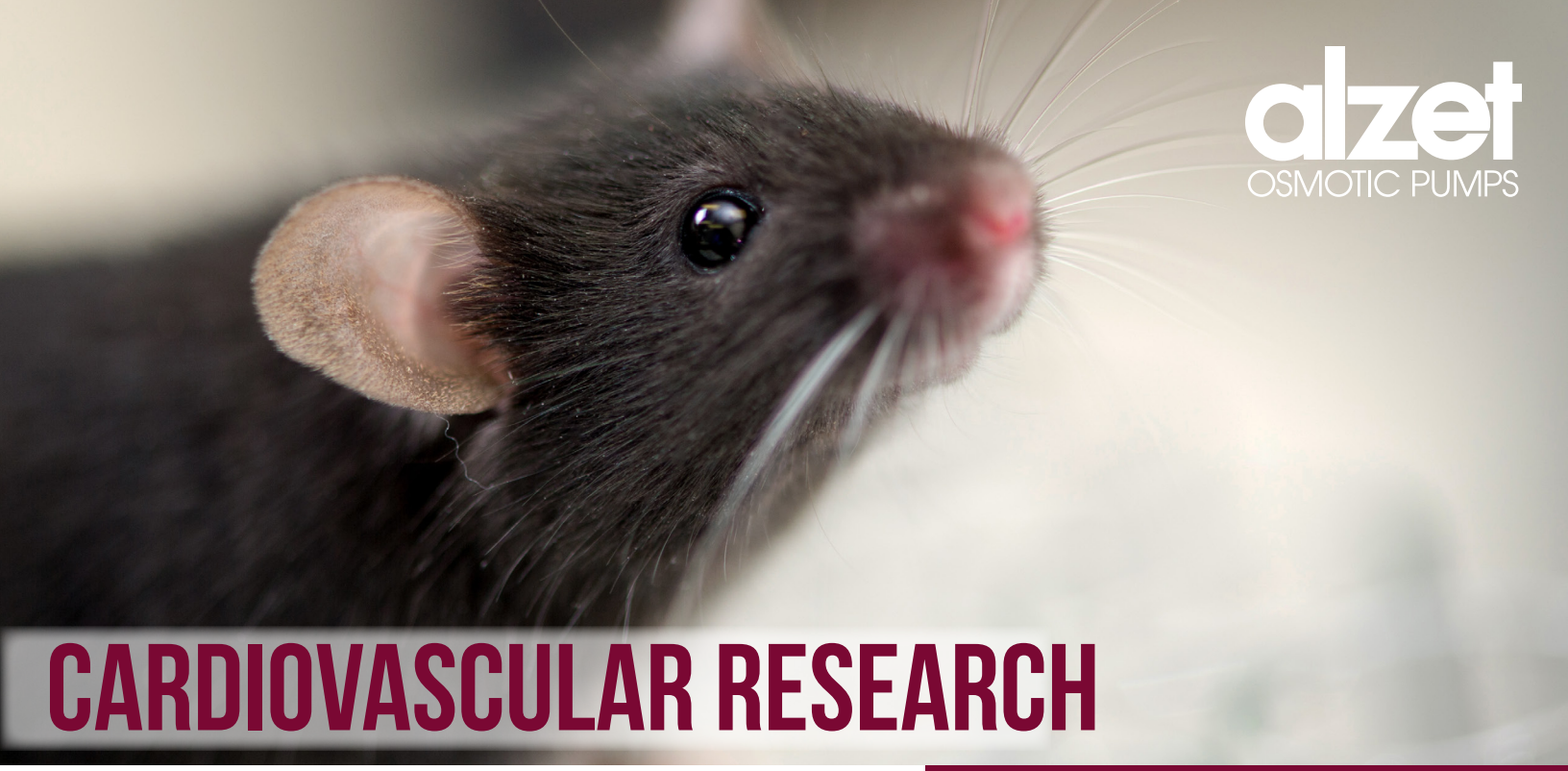
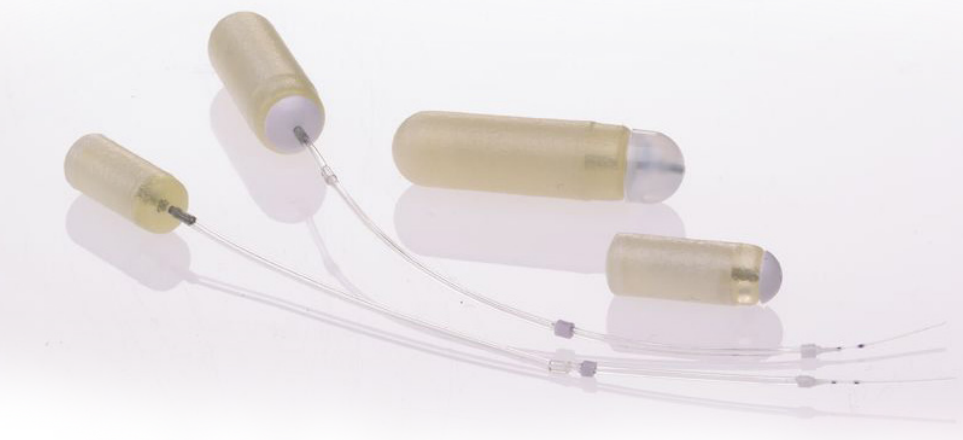


alzet
OSMOTIC PUMPS

CARDIOVASCULAR RESEARCH

According to the World Health Organization, cardiovascular diseases account for approximately 32% of all deaths worldwide, making cardiovascular diseases the leading cause of death globally.

In cardiovascular research, ALZET® Osmotic Pumps have played a significant role for several decades. Introduced in the 1970s, these osmotic pumps have long been widely utilized in various biomedical fields, including cardiovascular research. Their capability to deliver drugs in a controlled and continuous manner over extended periods has made them invaluable in studying cardiovascular diseases, unraveling underlying mechanisms, and investigating therapies.



Researchers have leveraged ALZET pumps in numerous studies to explore diverse aspects of cardiovascular function, pathology, and treatment strategies. The enduring use of ALZET pumps in cardiovascular research attests to their effectiveness and versatility in this field.

ALZET Pump Benefits

- Small size for implantation in mice or larger animals
- Continuous and controlled delivery of hypertensive agents
- Improved bioavailability of short half-life peptides and proteins
- Easy attachment to a catheter for delivery to the heart, arteries, or veins
- Reliable technology with over 22,000 publications
- Reduced drug toxicity and side effects compared to other chronic dosing methods
- Simple design and easy to use
- Improved animal welfare compared to other chronic dosing methods
- Convenient and cost-effective for chronic dosing of lab animals
- Automatic nighttime and weekend dosing

Cardiovascular Research Applications

Abdominal Aortic Aneurysm (AAA)

Over the past couple of decades, angiotensin II infusion via subcutaneous ALZET pumps has become the most common way of inducing AAA in animal models. For this model, the ApoE -/- knock-out mouse (C57BL/6 background) is preferred for its susceptibility to AAA since it lacks the gene to produce apolipoprotein E, leading to high levels of circulating cholesterol and eventual atherosclerosis.

The combined effect of genetically induced hypercholesterolemia and chemically induced hypertension via ALZET pump makes it a reliable and reproducible model for AAA. Researchers have used it for comprehensive investigation of AAA pathogenesis, encompassing aneurysm formation, progression, rupture, and associated molecular and cellular changes. Most importantly, the platform is allowing researchers to pursue new therapeutic strategies, such as agents that influence smooth muscle cell phenotype and other aspects of vessel integrity, repair and remodeling.

Atherosclerosis

The ApoE-/- mouse serves as a valuable tool for studying the development and progression of atherosclerotic plaques, as well as exploring potential therapies. In this model, ALZET pumps are utilized to deliver angiotensin II or other pro-inflammatory agents, such as lipopolysaccharides. By enabling long-term delivery of these agents, the pumps simulate the conditions contributing to the progression of atherosclerosis. While using the ApoE-/- mouse, researchers noticed that it was also exhibiting characteristics of hypertension.

In the late 1990s, a mouse model of hypertension was established with the ApoE-/- mouse to study the relationship between atherosclerosis and hypertension.

Hypertension Mouse Model

One of the most common utilizations of ALZET pumps is to deliver angiotensin II to induce hypertension. This model is instrumental in studying the development and progression of hypertension at the organ, tissue, and molecular level, as well as providing a platform for the evaluation of therapeutics.

Heart Failure

ALZET pumps have proven invaluable over many years in the study of heart failure, a complex clinical syndrome which commonly results from ischemic heart disease, hypertension, chronic obstructive pulmonary disease, or rheumatic heart disease. The progression of heart failure, such as following an ischemic insult from thrombotic plaque fragments or coronary embolism, involves cardiac remodeling characterized by an array of molecular, cellular and interstitial changes. Recent research in heart failure continues to demonstrate a clear role for ALZET pumps in ongoing work to understand the pathophysiological mechanisms, identify therapeutic targets and evaluate new treatments.

There are a variety of small animal models of heart failure, each developed for specific similarities with human pathology. Some, like surgical ligation or stenosis models, mimic injury that follows an embolic or thrombotic event, using permanent or transient surgical occlusion of the aorta or a coronary artery. Other methods, such as transverse aortic constriction, set up the left ventricular pressure overload associated with chronic hypertension. In these models, ALZET pumps have been used to deliver agents under evaluation for potential cardioprotective effects, such as:

- Ubiquitin, in a mouse ischemia-reperfusion model
- Serelaxin, in a mouse permanent ligation model
- MOTs-c peptide, in a mouse transverse aortic constriction model

Drug-induced models of heart failure are also widely employed, and in these, ALZET pumps play a direct role in establishing the model itself. Common protocols use chronic delivery of angiotensin II or isoproterenol by ALZET pump to reliably cause cardiac hypertrophy, dilation and ventricular dysfunction. Chronic ALZET administration of the cardiotoxic agent doxorubicin results in dilated cardiomyopathy characterized by cardiac remodeling that includes cardiomyocyte disarray and fibrotic lesions.

Incorporating genetically modified mice has enabled researchers to tease out cardioprotective genes, and ALZET pumps contribute here as well. For example, in a knockout expected to be cardioprotective, ALZET pumps have been used to replace the missing protein as a positive control, thus helping to identify a potential therapeutic target.

Heart failure is a global burden and its high mortality makes clear the need for more effective therapies. ALZET pumps offer a reliable and effective method for precise drug delivery, enabling advancements in understanding and treating this complex cardiovascular condition.

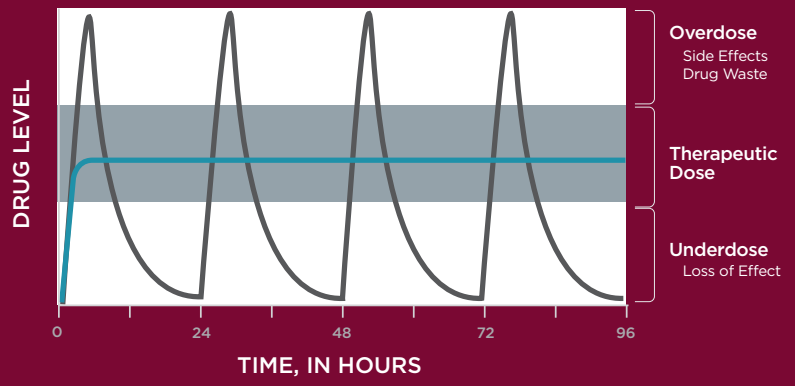
Pump use in Published Studies

ALZET pumps have successfully delivered over 8700 unique test agents to date. In cardiovascular research these include, but are not limited to, gene constructs, vasoactive peptides, growth factors, and inhibitors/activators of signaling pathways. Every day, researchers are trusting this reliable device to deliver test agents that have never been used before. Below is a list of test agents recently delivered with the pumps in cardiovascular studies.

Agent	Description
Angiotensin II	Vasoactive peptide hormone
Fibroblast growth factor 23, recombinant rat	Bone-derived hormone
Aldosterone	Steroid hormone
Ubiquitin	Protein
Ac-SDKP	Endogenous hemoregulatory peptide
Irisin	Thermogenic adipomyokine
MOTS-c	Mitochondial-derived peptide
Isoproterenol/Isoprenaline	Non-selective β adrenergic receptor agonist
ELA-21	Peptide
Soluble fms-like tyrosine kinase 1	Angiopoietin receptor
Relaxin, recombinant human	Hormone
Arginine vasopressin	Vasoconstrictor and antidiuretic hormone
Serelaxin	Protein hormone

The power of continuous delivery

Injections can result in great variations in serum and tissue concentrations. Immediately after injection, test agent concentrations commonly exceed effective levels, resulting in overdosing and toxicity. Between injections, concentrations can fall to ineffective levels in serum and tissues, resulting in underdosing and lack of effect. ALZET pumps deliver test agents at controlled and predictable rates, ensuring that constant and optimum levels are maintained throughout the study duration.



Why cardiology researchers use ALZET pumps in their studies

ALZET Benefit	
Chronic treatment Bypass the BBB	"We chronically applied a selective mGluR2/3 antagonist, LY341495, into the dorsal medulla oblongata with the aid of an osmotic pump...as NTS microinjection of the mGluR2/3 antagonist could also decrease mean blood pressure by approximately 18 mmHg in normotensive rats, the current study was considered very important for understanding pathophysiological mechanisms of blood pressure regulation." *Hsu et al. Life (Basel), 2021;11(7):720 p.2*
Create disease model Chronic delivery	"The AAA model induced by angiotensin (Ang) II was generated as follows: Micro-osmotic pumps containing saline (isotonic sodium chloride solution) or Ang II were subcutaneously implanted in 12-week-old male mice at 1000 ng/(kg min) for 28 days...Since the characteristics of Ang II-induced AAAs are consistent with activation of the inflammatory response and stimulation of protein hydrolysis cascade reaction, we used the Ang II-infused mouse model in this study." *Yang et al. Translational Research: the Journal of Laboratory and Clinical Medicine, 2023;255:85-96 p.2*
No Stress	"Ang II was administered by an ALZET osmotic pump, which could release Ang II continuously, homogeneously and stably; avoid stress due to repeated administration; and protect the short half-life of the drug." *Feng et al. Annals of Translational Medicine, 2021;9(3):207 p.3*

ALZET Products for Cardiologists

ALZET Osmotic Pumps
Twelve pump models available in 3 different sizes. Durations range from 1 day to 6 weeks with various release rates. Made in the USA.

Wound Closure Systems
The AutoClip & Reflex wound closure systems provide a fast and effective alternative to sutures for closing incisions.

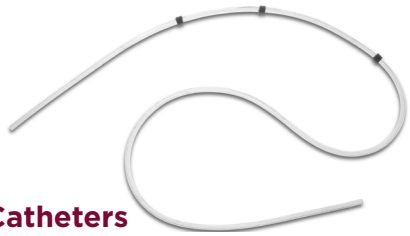
Specialized Catheters

Constructed with high quality materials for increased patency and reduced tissue trauma. These catheters are specifically designed to be used with all models of ALZET pumps.

Mouse Femoral Catheters
Features include: flexible and secure catheter junctions to minimize kinking and leaking; retention beads.

Mouse Jugular Catheters
Features include: retention beads; marks at 9 and 11mm for simplified adaptation. Three options to choose from: regular, adjustable length, and large-tip.

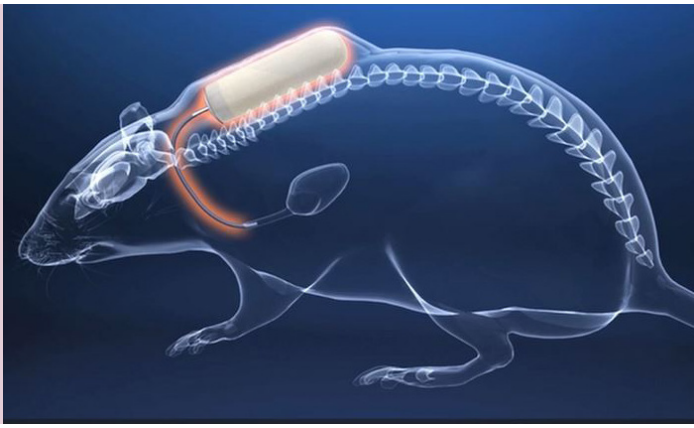
Rat Jugular Catheters
Features include: silicone patch for anchoring; bevel tip.



Rat Femoral Catheters
Features include: flexible and secure catheter junctions to minimize kinking and leaking; retention beads. Two options to choose from: standard and tapered.

Access ALZET surgical implantation procedures online!

Video: www.vimeo.com/channels/alzet
Written: www.alzet.com/resources/downloads/#surgical-sheets



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