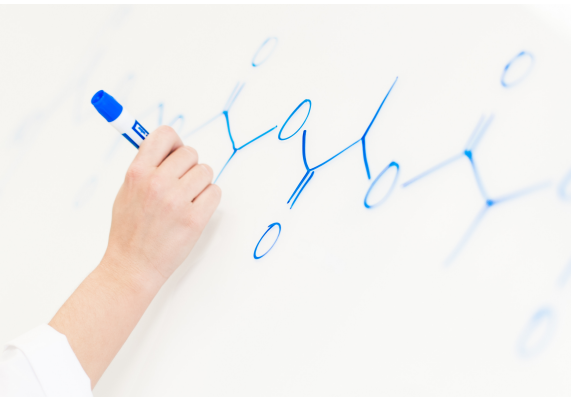
ALZET Research Application

Translational Research



Translational research is a bi-directional process in which scientific knowledge is used to direct clinical development and clinical knowledge used to drive basic research. This strategy aims to accelerate the pace at which novel research discoveries are translated into safe and effective clinical therapies.

Effective translation of therapeutic strategies from the experimental phase into the clinic is often dependent on the availability of suitable animal models that closely mimic clinical features. Equally important is the use of reliable research tools to ensure reproducible study results. ALZET Osmotic Pumps are useful drug delivery tools for translational research and drug development. These small infusion pumps have been used in translational research studies designed to evaluate drug pharmacokinetics, safety and tolerability. They are also used in dose escalation studies designed to determine the maximum starting dose or effective therapeutic dose. Compared to conventional dosing methods, ALZET pumps allow greater control and accuracy in drug delivery, thus reducing dosing errors, ensuring stable dose levels and minimizing adverse effects. Most importantly, they help generate reliable preclinical data that can then be applied to clinical studies with greater confidence.

Listed below are two case studies describing the use of ALZET pumps in translational research. Additional references are available from ALZET Technical Services at 800.692.2990 or alzet@durect.com.

ALZET Applications in Translational Research

- *Pharmacokinetic studies*
- *In vivo drug efficacy*
- *Drug safety and tolerability*
- *Dose escalation studies*
- *Maximum starting dose estimation*
- *Evaluation of optimal dosing schedules*

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alzet® OSMOTIC PUMPS

Case Study #1

Publication	Kumar *et al.* Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. Mol Cancer Ther 2007;6(7):2012–2021
Therapeutic Area	• Cancer
Agents	• Pazopanib analog (GW771806); VEGF receptor inhibitor; c-Kit tyrosine kinase inhibitor
Purpose of Study	• Determine optimal dose for in vivo antitumor and antiangiogenic activity • Compare drug pharmacokinetics by two routes of administration: oral bolus and continuous infusion

Brief Methods	• GW771806 (a pazopanib analog) used for its improved solubility properties
	• Nude mice treated with various doses of GW771806 by oral gavage or continuous infusion with ALZET pumps (Model 2001)
	  • Oral dose: 100, 30, 10, or 3 mg/kg BID
	  • Continuous dose: 10, 3, or 1 mg/kg/day
	• Animals evaluated for plasma levels, tumor inhibition and anti-angiogenic activity

Significant Findings	• Steady-state plasma concentration (2.57 mmol/L at 10 mg/kg/day) from continuous dosing was more effective than maximum concentration (>20 mmol/L) achieved with 10 and 30 mg/kg BID oral dosing • Dose-dependent inhibition of tumor growth and angiogenesis observed following pazopanib analog administration
Clinical Relevance	• PK/PD effects and antitumor activity validated in phase I clinical trial • Study indicates that preclinical models can be used to guide pharmacokinetic-based dose selection for VEGFR inhibitors in clinical studies • Pazopanib is currently being studied in multiple clinical trials as a single agent and in combination with other agents

Case Study #2

Publication	Trevaskis *et al*. Amylin-Mediated Restoration of Leptin Responsiveness in Diet-Induced Obesity: Magnitude and Mechanism. Endocrinology 2008;148(11):5679-5687
Therapeutic Area	• Obesity
Agents	• Amylin and Leptin (peptide hormones)
Purpose of Study	• Evaluate the synergistic action of amylin and leptin on food intake and body weight • Investigate the amylin/leptin dose response at lower ranges than those used during single therapy

Brief Methods	• Rats were implanted with two ALZET pumps containing either drug or vehicle
	• Amylin and leptin were administered for 4 weeks
	  • Amylin doses: 0, 10, 50 µg/kg/day
	  • Leptin doses: 0, 5, 25, 125 µg/kg/day
	• Plasma leptin and amylin concentrations measured after the 4 week treatment

Significant Findings	• Synergistic relationship between amylin and leptin for both food intake inhibition and weight loss • Maximum effect found at 50 µg/kg/day (amylin) plus 125 µg/kg/day (leptin) dose combination • Weight loss persisted over the 28-day period and occurred at considerably lower doses than previously tested
Clinical Relevance	• Dose selection study • Novel treatment option for obesity

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