

Recent References (2015-Present) on the Administration of Antisense Oligonucleotides Using ALZET® Osmotic Pumps

Q10992: A. Saoudi, *et al.* Investigating the Impact of Delivery Routes for Exon Skipping Therapies in the CNS of DMD Mouse Models. Cells 2023;12(6):

Agents: Oligonucleotides, antisense **Vehicle:** Not Stated; **Route:** CSF/CNS (intracerebroventricular); **Species:** Mice; **Strain:** hDMD; mdx52; **Pump:** 1002; **Duration:** 2 weeks;

ALZET Comments: Dose (~700 nmol); animal info: 6–8-week-old mdx52 and WT mice; comparison of bolus injection vs mp; neurodegenerative (neurological disorder); brain tissue distribution

Q10962: I. Michailidou, *et al.* The systemic inhibition of the terminal complement system reduces neuroinflammation but does not improve motor function in mouse models of CMT1A with overexpressed PMP22. Current Research in Neurobiology 2023;4(100077

Agents: Oligonucleotide, antisense **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Strain:** C3-PMP22 (C22-PMP22 x C57BL/6); **Pump:** 1007D; **Duration:** Not Stated;

ALZET Comments: Dose (5 mg/kg); Controls received mp w/ vehicle; animal info: C57Bl/6 mice; C6 LNA oligonucleotide targets mRNA of C6; neurodegenerative (Charcot-Marie-Tooth disease)

Q10459: E. O. Cruz-Lopez, et al. Blood pressure-independent renoprotective effects of small interference RNA targeting liver angiotensinogen in experimental diabetes. British Pharmacological Society 2023;180(1):80-93

Agents: Valsartan; Captopril Vehicle: Not Stated; Route: SC; Species: Rat; Pump: 2ML4; Duration: 3 weeks;

ALZET Comments: "Dose: Valsartan (4 mg-kg/day); Captopril (6 mg-kg/day); animal info: Male, heterozygous Ren2 rats (10-week-old; weight 300–500 g); Blood pressure measured via: radiotelemetry

transmitters; Blood pressure results see (pg.5)antihypertensive; antisense (Oligonucleotides); dependence; "

Q10379: L. A. Ezerskiy, *et al.* Astrocytic 4R tau expression drives astrocyte reactivity and dysfunction. JCI Insight 2022;7(1): **Agents:** Oligonucleotide, antisense **Vehicle:** Not Stated; **Route:** CSF/CNS (right ventricle); **Species:** Mice; **Pump:** Not Stated; **Duration:** Not Stated;

ALZET Comments: Dose (15 ug/d); animal info (hTau); Brain coordinates (1.1 mm lateral; 0.5 mm posterior; 2.5 mm ventral from bregma); neurodegenerative (); Therapeutic indication (neurodegenerative diseases); gene therapy

Q10284: H. Tran, et al. Suppression of mutant C9orf72 expression by a potent mixed backbone antisense oligonucleotide. Nature Medicine 2022;28(1):117-124

Agents: Oligonucleotide, antisense **Vehicle:** PBS; **Route:** CNS/CSF (intracerebroventricular); **Species:** Mice; **Pump:** 1007D; **Duration:** 21 days;

ALZET Comments: Dose (2.5-20 nmol/day); dose-response (dose-dependent reduction in V1 and V3 repeat-containing transcripts in both the cortex and spinal cord regions after being treated with ASO3 and ASO5); animal info (C9BAC transgenic mice); antisense oligonucleotides aka ASO; antisense (oligonucleotide); ALZET brain infusion kit 3 used; bilateral cannula used; 2.5-20 nmol/day of each ASO were continuously infused over 10 d into the right lateral ventricle of age-matched heterozygous C9BAC mice through a cannula using an implanted Alzet osmotic pumptissue perfusion (brain); neurodegenerative (ALS);(FTD) Therapeutic indication (ALS, FTD);

Q10315: D. Ruiz, et al. Sex-based eRNA expression and function in ischemic stroke. Neurochemistry International 2021;150(105149

Agents: Oligonucleotides **Vehicle:** CSF, artificial; **Route:** CSF/CNS (intracerebral venticular); **Species:** Mice; **Pump:** 1003D; **Duration:** 24 hours;

ALZET Comments: Dose: (8.3 pmol/ul); Controls received mp w/ vehicle; animal info: 3-months-old female C57BL/6N mice weighing an average 20.5 g and 3-months-old male C57BL/6N mice weighing on average 22.7 g; (Alzet Brain Infusion Kit 3, DURECT Corporation used; Brain coordinates ((Bregma: 0.2 mm posterior, 0.9 mm lateral, and 2/5 mm dorsoventral); ischemia (Ischemic stroke);





Q8701: S. Bhattarai, *et al.* Modulation of Brain Pathology by Enhancer RNAs in Cerebral Ischemia. Mol Neurobiol 2021;58(4):1482-1490

Agents: Anti-eRNA oligos **Vehicle:** CSF/ artificial; **Route:** CNS/CSF; **Species:** Mice; **Pump:** 1003D; **Duration:** 3 days; **ALZET Comments:** Dose (8.3 pmole/ul); animal info (3 months old, 20-30 g, C57BL/6N); antisense (eRNA_06347:

5'-GATTTGGAATTGCTAG-3'; eRNA_093384: 5'-GGAAGCAGGTGAACAG-3'); ALZET brain infusion kit 3 used; ischemia (Cerebral);

Q9846: Y. Zhang, *et al.* WWP2 regulates SIRT1-STAT3 acetylation and phosphorylation involved in hypertensive angiopathy. Journal of Cellular and Molecular Medicine 2020;24(16):9041-9054

Agents: miR-155 inhibitor **Vehicle:** CSF, Artificial; **Route:** CSF/CNS; **Species:** Rat; **Pump:** Not Stated; **Duration:** Not Stated; **ALZET Comments:** Controls received mp w/ vehicle; animal info (Sprague Dawley, 200-250 g); antisense (5'AAU UAC GAU UAG CAC UAU CCC CA-3'); ALZET brain infusion kit XX used; Brain coordinates (3.7mm posterior to the bregma, 4.1mm lateral to the midline, and 3.5mm under the dura); bilateral cannula used; dental cement used; neurodegenerative (Intracerebral Hemorrhage);

Q9463: X. Shi, et al. MiR-144-5p limits experimental abdominal aortic aneurysm formation by mitigating M1 macrophage-associated inflammation: Suppression of TLR2 and OLR1. Journal of Molecular and Cellular Cardiology 2020;143(1-14

Agents: Oligodeoxynucleotide, phosphorothioate; Oligodeoxynucleotide, phosphorothioate antisense **Vehicle:** Not Stated;

Route: SC; Species: Mice; Rat; Pump: Not Stated; Duration: 14 days;

ALZET Comments: Dose (90 ng/g of body weight/day); animal info (8-week-old male C57BL/6 mice, 21-26 g; rats, 200-250 g); diabetes;

Q8370: M. Popek, *et al.* Physiology and Morphological Correlates of Excitatory Transmission are Preserved in Glutamine Transporter SN1-Depleted Mouse Frontal Cortex. Neuroscience 2020;446(124-136

Agents: Anti-SN1 vivo-morpholinos oligonucleotides **Vehicle:** Saline; **Route:** CNS/CSF; **Species:** Mice; **Pump:** 1002; **Duration:** Not stated;

ALZET Comments: Dose (1.2 mg/kg/day); Controls received mp w/ vehicle; animal info (Male, C57Bl6, 30 g); peptides; Brain coordinates (AP + 2.0, ML 0.8, DV 1.5)); neurodegenerative (Glutamatergic transmission);

Q8343: N. Bai, *et al.* G-protein-coupled estrogen receptor activation upregulates interleukin-1 receptor antagonist in the hippocampus after global cerebral ischemia: implications for neuronal self-defense. J Neuroinflammation 2020;17(1):45 **Agents:** G1; G36; Oligodeoxynucleotide, IL1RA antisense; Scrambled Missense **Vehicle:** DMSO; Saline; **Route:** SC; CNS/CSF (left lateral ventricle); **Species:** Rat; **Pump:** 2004; 2002; 2001; **Duration:** 14 days;

ALZET Comments: Dose (10 ug/day; 10 nmol/day); 1% DMSO, 0.9% saline used; Controls received mp w/ vehicle; animal info (Adult female Sprague-Dawley rats); G1 aka GPER agonist; G36 aka GPER antagonist; ALZET brain infusion kit Lot no 10331-14 used; Brain coordinates (anteroposterior, 0.8 mm; lateral, 1.5 mm; depth, 3.5 mm; from bregma); ischemia (GPER neuroprotective effects);

Q8332: D. Alarcon-Aris, et al. Anti-alpha-synuclein ASO delivered to monoamine neurons prevents alpha-synuclein accumulation in a Parkinson's disease-like mouse model and in monkeys. EBioMedicine 2020;59(102944

Agents: Oligonucleotides, antisense **Vehicle:** CSF, artificial; **Route:** CNS/CSF (lateral ventricle); **Species:** Mice; Monkey (rhesus macaques); **Pump:** 1004; 2ML4; **Duration:** 28 days;

ALZET Comments: Dose (30 ug/day; 100 ug/day; 1 mg/day); Controls received mp w/ vehicle; animal info (Eight-week-old wild-typle male C57BL/6J mice; male and female rhesus macaques, 20 years or older); antisense oligonucleotides aka IND-ASO; ALZET brain infusion kit 3 used; Brain coordinates (antero-posterior -0.34, medial-lateral -1.0 and dorsal-ventral -2.2 in mm); neurodegenerative (Parkinson's disease);

Q8007: V. Gerzanich, et al. Sulfonylurea Receptor 1, Transient Receptor Potential Cation Channel Subfamily M Member 4, and KIR6.2:Role in Hemorrhagic Progression of Contusion. J Neurotrauma 2019;36(7):1060-1079

Agents: Antisense oligodeoxynucleotides **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** Not stated; **ALZET Comments:** Dose (400 ng/h); Controls received mp w/ vehicle; animal info (Male, Wistar, 12-16 weeks old, 325-400 g); Antisense oligodeoxynucleotides aka AS-ODN; antisense (Antisense oligodeoxynucleotides); neurodegenerative (Traumatic Brain Injury);





Q8158: P. Alvarez, et al. Unpredictable stress delays recovery from exercise-induced muscle pain: contribution of the sympathoadrenal axis. Pain Rep 2019;4(5):e782

Agents: Epinephrine Vehicle: Saline; Route: SC; Species: Rat; Pump: 2004; Duration: 2 weeks;

ALZET Comments: Dose (5.4 mg/0.25 mL/h); Controls received mp w/ vehicle; animal info (adult male Sprague-Dawley rats, weighing 250 to 400 g (approximately 8-12 weeks old)); antisense (intrathecal b2-adrenergic receptor antisense);

R0389: S. M. Pulst, *et al.* 2017 Year in Review and Message from the Editors to Our Reviewers. Neurol Genet 2018;4(1):e221 **Agents:** Oligonucleotide, antisense **Vehicle:** Not Stated; **Route:** CSF/CNS (Lateral Ventricle); **Species:** Mice; **Pump:** Not Stated; **ALZET Comments:** neurodegenerative (tau pathology); Therapeutic indication (neurodegenerative disease);

Q7231: I. Michailidou, *et al.* Systemic inhibition of the membrane attack complex impedes neuroinflammation in chronic relapsing experimental autoimmune encephalomyelitis. Acta Neuropathologica Communications 2018;6(1):36

Agents: Oligonucleotide, antisense Vehicle: PBS; Route: SC; Species: Mice; Pump: 1002; Duration: 14 days;

ALZET Comments: Dose (5 mg/kg); animal info (Male 7 to 8-week-old Biozzi AB/H mice, 26.93 ± 0.33 g); C6 antisense aka c6 Locked nucleic acid oligonucleotide; antisense (C6); immunology;

Q6747: N. Prakoura, et al. NFkappaB-Induced Periostin Activates Integrin-beta3 Signaling to Promote Renal Injury in GN. J Am Soc Nephrol 2017;28(5):1475-1490

Agents: Oligonucleotide, antisense **Vehicle:** Saline; **Route:** SC; **Species:** Mice (knockout); **Pump:** 1002; **Duration:** Not Stated; **ALZET Comments:** Dose (0.25 ml/h or 150 pmol/day); animal info (SV129malewild-typemice aged 8–10 weeks); antisense (periostin)

Q6035: A. J. Donner, *et al.* Co-Administration of an Excipient Oligonucleotide Helps Delineate Pathways of Productive and Nonproductive Uptake of Phosphorothioate Antisense Oligonucleotides in the Liver. Nucleic Acid Ther 2017;27(4):209-220 **Agents:** Oligonucleotide, antisense **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 2001D; **Duration:** 1 day; **ALZET Comments:** Controls received mp w/ vehicle; animal info (C57BL/6); Therapeutic indication (hepatocytes); Dose (10 uL/body weight);

Q6600: C. Mazur, *et al.* Development of a simple, rapid, and robust intrathecal catheterization method in the rat. J Neurosci Methods 2017;280(36-46

Agents: Oligonucleotide, antisense **Vehicle:** Not Stated; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** Not Stated; **ALZET Comments:** animal info (Sixteen male Sprague-Dawley rats); Publication describes the development of a rapid and robust intrathecal catheterization method for the testing of putative ASO therapeutics for diseases of the CNS.

Q5785: S. Devos. Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy. Science Translational Medicine 2017;9(374):

Agents: Oligonucleotide, antisense (Tau-specific) **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** Mice; **Pump:** Not Stated; **Duration:** 28 days, 4 weeks;

ALZET Comments: Controls received mp w/ scrambled ASO, or vehicle; animal info (PS19 mice); antisense (Tau-specific ASO-12); neurodegenerative (Alzheimer's disease); Therapeutic indication (Alzheimer's disease, tauopathy); Dose (30 ug/day);

Q5474: A. Vikram, *et al.* Vascular microRNA-204 is remotely governed by the microbiome and impairs endothelium-dependent vasorelaxation by downregulating Sirtuin1. Nat Commun 2016;7(12565

Agents: Oligonucleotide, anti-miR-204 Species: Mice; Pump: 2006; Duration: 6 weeks;

ALZET Comments: Controls received mp w/ scrambled oligonucleotides; animal info (male, eSirt1 -/- or C57BL6); cardiovascular; Dose (0.7 mg/kg/day);

Q6041: L. German-Castelan, et al. Intracellular Progesterone Receptor Mediates the Increase in Glioblastoma Growth Induced by Progesterone in the Rat Brain. Archives of Medical Science 2016;47(6):419-426

Agents: Oligodeoxynucleotide, antisense Vehicle: Propylene glycol; Route: CSF/CNS; Species: Rat;: 15 days;

ALZET Comments: animal info (250-300g); tissue perfusion (brain tissue); Guide cannula used; Therapeutic indication (Astrocytomas, CNS tumor); Dose (0.5 ug/day);





Q5207: Y. Solomonov, et al. Reduction of cytosolic phospholipase A2alpha upregulation delays the onset of symptoms in SOD1G93A mouse model of amyotrophic lateral sclerosis. J Neuroinflammation 2016;13(1):134

Agents: Oligonucleotide, antisense anti-Cytosolic phospholipase A2 alpha **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** Mice (transgenic); **Pump:** Not Stated; **Duration:** 4 weeks; 6 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, B6.Cg-Tg(SOD1G93A)1Gur/J hemizygous transgenic, 10 weeks old, 25 g); ALZET brain infusion kit 3 used; antisense (oligonucleotide anti-Cytosolic phospholipase A2 alpha); neurodegenerative (amyotrophic lateral sclerosis); behavioral testing (rotarod test; ladder testing); pumps primed overnight in 37C saline; Dose (10 ug/day); Brain coordinates (right lateral cerebral ventricle (–1.0 mm mediolateral and –0.5 mm anteroposterior from Bregma));

Q5197: K. M. Schoch, *et al.* Increased 4R-Tau Induces Pathological Changes in a Human-Tau Mouse Model. Neuron 2016;90(5):941-7

Agents: Oligonucleotides, antisense **Vehicle:** Not Stated; **Route:** CSF/CNS; **Species:** Mice (transgenic); **Duration:** 28 days; **ALZET Comments:** Controls received mp w/ saline or scrambled ASO; animal info (hTau transgenic or tau N279k transgenic, 3-4 months old); antisense (3R to 4R MAPT splicing ASO; 4R to 3R MAPT splicing ASO); neurodegenerative (Alzheimer's disease); behavioral testing (nesting behavior); cyanoacrylate adhesive; pumps primed in 37C saline overnight; Industry authored (lonis Pharmaceuticals); Dose (14 ug/day for 3R to 4R MAPT splicing ASO; 25 ug/day for 4R to 3R MAPT splicing ASO); Brain coordinates (-1.1mm M/L, -0.5mm A/P, -2.5mm D/V from bregma supplement pg 5);

Q5622: D. Kim. Anti-miR delivery strategies to bypass the blood-brain barrier in glioblastoma therapy. Oncotarget 2016;7(20):29400-11

Agents: Oligonucleotide, anti-miR, anti-let-7 **Vehicle:** Saline; **Route:** CSF/CNS (intrathecal); **Species:** Mice; **Pump:** 1004D; **Duration:** 7 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (6-7 weeks); ALZET brain infusion kit 3 used; "Among them, the osmotic pump system is one of the most useful convection-enhanced delivery methods for delivering drugs to brain tumors and bypassing the BBB" pg 29408; Dose (20 μ M, 50 μ M); good figures (p29402;

Q5348: J. D. Figueroa, *et al.* Fatty Acid Binding Protein 5 Modulates Docosahexaenoic Acid-Induced Recovery in Rats Undergoing Spinal Cord Injury. J Neurotrauma 2016;33(15):1436-49

Agents: Oligonucleotides, scramble nontargeting; siRNA **Vehicle:** Ethanol; **Route:** CSF/CNS (Intrathecal); **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (Young adult female Sprague-dawley rats); good methods (pg 1443); spinal cord injury; "Pumps were primed with DHA-albumin complex (DHA), FABP5 siRNA, and vehicle controls" (pg 1443); ALZET rat intrathecal catheter used;

Q5805: S. Eid, *et al.* mTORC2 Signaling Regulates Nox4-Induced Podocyte Depletion in Diabetes. Antioxidants & Redox Signaling 2016;25(13):703-719

Agents: Oligonucleotide, phosphorothioate antisense (Rictor); Oligonucleotide, phosphorothioate sense (Rictor); **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2006; **Duration:** 5 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (17 weeks old)antisense (phosphorothioated Sense and Antisense for Rictor); diabetes; Therapeutic indication (Diabetes);Dose (90 ng*g body wt-1 * day-1),);

Q5754: R. Boukari, *et al.* Membrane progesterone receptor-beta, but not -alpha, in dorsal brain stem establishes sex-specific chemoreflex responses and reduces apnea frequency in adult mice. J Appl Physiol (1985) 2016;121(3):781-791

Agents: RNA, small interfering **Vehicle:** CSF, artificial; **Route:** CSF/CNS (fourth ventricle); **Species:** Mice; **Pump:** 1002; **Duration:** 2 weeks, 14 days;

ALZET Comments: Controls received mp w/ vehicle; animal info (3-4 months old); antisense (siRNA against MPR-a or mPR-b); "Previous studies

in adult mice showed that 2-wk infusion of nonviral siRNA in the third ventricle ensured efficient (_50%) and widespread (5–6 mm around the infusion point) knockdown of target genes in the brain (48)." Pg 782; Therapeutic indication (Sex steroids, Chemoreflex);





Q4223: X. Zhang, et al. Prosurvival NMDA 2A Receptor Signaling Mediates Postconditioning Neuroprotection in the Hippocampus. Hippocampus 2015;25(286-296

Agents: Oligonucleotide, antisense NR2A **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 1007D; **Duration:** Not Stated; **ALZET Comments:** Controls received mp w/ scrambled oligonucleotide; animal info (male, Sprague Dawley, adult, 250-300g); antisense (oligonucleotide NR2A);

Q4976: F. A. Oladosu, *et al.* Mu Opioid Splice Variant MOR-1K Contributes to the Development of Opioid-Induced Hyperalgesia. PLoS One 2015;10(8):e0135711

Agents: RNA, small interfering 13 antisense **Vehicle:** CSF, artificial; **Route:** CSF/CNS (intrathecal); **Species:** Mice; **Pump:** Not Stated; **Duration:** 7 days;

ALZET Comments: Controls received mp w/ sense siRNA; animal info (C57BL6J or CXB7/ByJ, 8-12 weeks old, 20-30g);

Q4640: M. Wellman, *et al.* Knockdown of central ghrelin O-acyltransferase by vivo-morpholino reduces body mass of rats fed a high-fat diet. PEPTIDES 2015;70(17-22

Agents: Oligonucleotide, antisense vivo-morpholino **Vehicle:** PBS; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2004; **Duration:** 4 weeks;

ALZET Comments: Controls received mp w/ vehicle; animal info (male, Long Evans, 276-300g); Cannula placement verified via injection of dye;

Q4648: H. K. A. Wong, et al. The Cancer Genome Atlas Analysis Predicts MicroRNA for Targeting Cancer Growth and Vascularization in Glioblastoma. MOLECULAR THERAPY 2015;23(1234-1247

Agents: RNA, micro antisense inhibitors 2'-O-MOE-PO **Vehicle:** Not Stated; **Route:** CSF/CNS (striatum); **Species:** Mice (nude); **Pump:** 2004; **Duration:** 30 days; 60 days;

ALZET Comments: Animal info (nude, 8 weeks old); pumps replaced every 30 days; ALZET brain infusion kit 3 used; "To ensure efficient and continuous local delivery of either miR-31 or miR-148a inhibitors to the intracranial tumors, and avoid repeated neurosurgeries, we used osmotic pumps" pg 1236; picture of implanted pump pg 1238;

Q5279: Y. Sztainberg, *et al.* Reversal of phenotypes in MECP2 duplication mice using genetic rescue or antisense oligonucleotides. Nature 2015;528(7580):123-6

Agents: Oligonucleotide, antisense MECP2 **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** mice; **Pump:** 1004; **Duration:** 28 days; **ALZET Comments:** Controls received mp w/ vehicle; animal info (FVB/N pure background); functionality of mp verified by EEG; ALZET brain infusion kit 3 used; ALZET brain infusion kit 3 used; good methods (pg. 6); gene therapy; Dose (500 ug); Brain coordinates; AP = -0.2 mm, ML = 1 mm, DV = -3 mm

Q4800: K. B. a. T. E. Spencer. Biological Roles of Interferon Tau (IFNT) and Type I IFN Receptors in Elongation of the Ovine Conceptus 1. Biology of Reproduction 2015;92(2)(47):1-10

Agents: oligonucleotides, antisense morpholino **Vehicle:** PBS; **Route:** Intrauterine; **Species:** Sheep (ewe, pregnant); **Pump:** 2ML1; **Duration:** 7 days;

ALZET Comments: Controls received mp w/ control oligonucleotides; animal info (female, Columbia Rambouillet); teratology; cyanoacrylate adhesive; used vinyl catheter tubing (0007760) to cannulate uterine lumen; pump affixed to mesosalpinx using cyanoacrylate glue;

Q5232: M. McMillin, *et al.* Suppression of the HPA Axis During Cholestasis Can Be Attributed to Hypothalamic Bile Acid Signaling. Mol Endocrinol 2015;29(12):1720-30

Agents: Oligonucleotide, Vivo-morpholino **Vehicle:** Not Stated; **Route:** CSF/CNS (lateral ventricle); **Species:** Rat; **Pump:** Not Stated; **Duration:** 3 days;

ALZET Comments: Controls received mp w/ vehicle; brain infusion kit used; brain tissue distribution; Dose (1 mg/kg / d);