Drug dosing regimens influence outcomes.

Application Examples
from peer reviewed publications and webinars

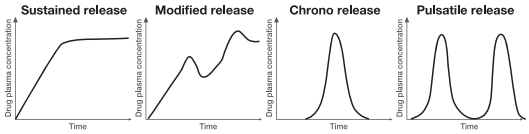
More translational preclinical models

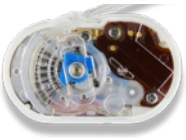
Micro infusion pump

iPRECIO®

Implantable, Programmable and Refillable

SMP-200
1ul/hr 6months





SMP-310R
0.1ul/hr. 67.8days

All things mouse	Pg.26, 32 & 35	Neuroscience	Pg.9-12, 15, 17, 27-31
Cardiovascular	Pg.13 & 32-34	Metabolism	Pg.5-8
Clinical Regimens	Pg.36	Oncology	Pg.14, 16 & 22-27
GLP & Toxicology	Pg.21	Webinars	Pg.22-24, 31

Micro infusion pump

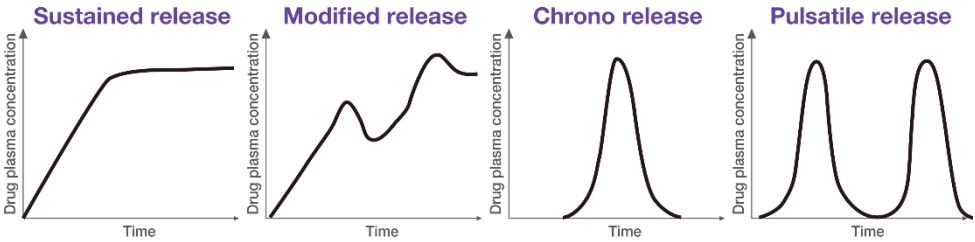
iPRECIO®

Implantable, Programmable and Refillable

iPRECIO Micro Infusion Pumps

<Off-the-shelf> development tool for use in drug discovery

1. Reduced drug requirements
2. Large selection of compatible solvents used in drug discovery
3. Easy to modulate and time exposure profiles with non-optimized compound
4. Easy to use/program
5. Available since 2007



- Solubility issues and need a higher flow rate?
- Need more control for dosage due to narrow therapeutic index?
- Want to program a drug holiday or maximize efficacy/reduce toxicity with a timed dose during the mornings?
- Want to refill with a different test article/drug (sequential administration)?

SMP-310R

SMP-200

The ability to program the device to start, stop and deliver different doses at different time points or just deliver one continuous dose makes iPRECIO ideally suited to the drug discovery and basic research process. All programmed in an easy to use PC based application software.

iPRECIO Micro Infusion Pumps for Drug Delivery

Exposure-enabling technology for advancing early preclinical studies and basic research

- Enables simple and complex dosing regimens at the click of the mouse/keyboard (ubiquitous PC) – several clicks
- Automation which minimizes animal handling
- Reduces stress and behavior anomalies
- Parenteral route which is practical and extremely important

Basic requirements

- Surgical skills/training (important for successful use of iPRECIO Micro Infusion Pumps)
- Basic computer skills/literacy

Resources available from Primetech

- Surgical training videos and step by step Surgical Technical Notes
- User Manual, workflows and step by step programming guide
- Compatible vehicle/solvents and easy to use compatibility test kit

What researchers are saying :

" Thank your company for developing this miniaturized programmable pump that has really been a game changer in this work (and promise to be of tremendous help in the field of Neuroendocrinology, Endocrinology and Metabolism in the future) and enabled the completion of preclinical studies in mice that paved the way to human clinical trials. "

Ease of programming: "I was pleasantly surprised with how easy it was to program, fill, and implant the pumps."

Programmable & implantable pump : "This device enables implementation of infusion protocols to reliably and precisely achieve the desired exposure profiles (shapes and timing) with low degree of invasiveness."

Improved drug delivery: "The infusion pumps enhanced the delivery of the drug and allowed for us to identify a clean behavioral antidepressant effect, devoid of complications due to daily injections."

Improved drug efficacy: "This study demonstrated that an equivalent effect was possible at a much lower dose than was previously studied (25µg/serotonin hydrochloride/kg/min) in the sham and DOCA–salt rat."

Reproducible results: "I have accumulated few more very nice recordings using iPrecio. Few recording are really breath-taking by reproducibility of responses."

"Your pump is AMAZING in terms of being able to do an intra-animal dose response curve. I absolutely, positively loved this. As a pharmacologist, there is nothing better."

Lead Optimization Study: "…we use them for studies to understand the PK-PD relationship of specific molecules. In terms of the infusion protocol it would be multiple steps to achieve a specific PK concentration in a PD study."

Things went well with the last iPRECIO study. The pumps did a fantastic job as they were programmed to do. iPRECIO data were in line with predicted/calculated values. As a matter of fact, we are in the process of completing another study using the iPRECIO pumps.

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   - b Dosing Profile Profoundly Influences Nicotinic Acid's Ability to Improve Metabolic Control in Rats
   - c The abruptness of terminating nicotinic acid delivery has a profound effect on free fatty acid and insulin rebound in rats, 51st EASD Annual Meeting, Stockholm 2015
   - d Ecto-domain phosphorylation promotes functional recovery from spinal cord injury, Scientific Reports
   - e Intrathecal administration using the iPRECIO® implanted pump
   - f Enhanced Resistance to Permeability Transition in Interfibrillar Cardiac Mitochondria in Dogs: Effects of Aging and Long Term Aldosterone Infusion, American Journal Of Physiology
   - g Highly Effective Auger-Electron Therapy in an Orthotopic Glioblastoma Xenegraft Model using Convection-Enhanced Delivery
   - h Chronic intermittent convection-enhanced delivery of vigabatrin to the bilateral subthalamic nucleus in an acute rat seizure model.
   - i Early Stage Preclinical Formulation Strategies to Alter the Pharmacokinetic Profile of Two Small Molecule Therapeutics
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Research Applications 1

SC Administration

Timed release of Test Article (TA), ßOHB

Rohit Chavan, Céline Feillet, Sara S. Fonseca Costa, James E. Delorme, Takashi Okabe, Jürgen A.Ripperger & Urs Albrecht
Liver-derived ketone bodies are necessary for food anticipation.
Nature Communications 7, Article number: 10580 doi:10.1038/ncomms10580
http://www.nature.com/ncomms/2016/160203/ncomms10580/full/ncomms10580.html?WT.ec_id=NCOMMS-20160205

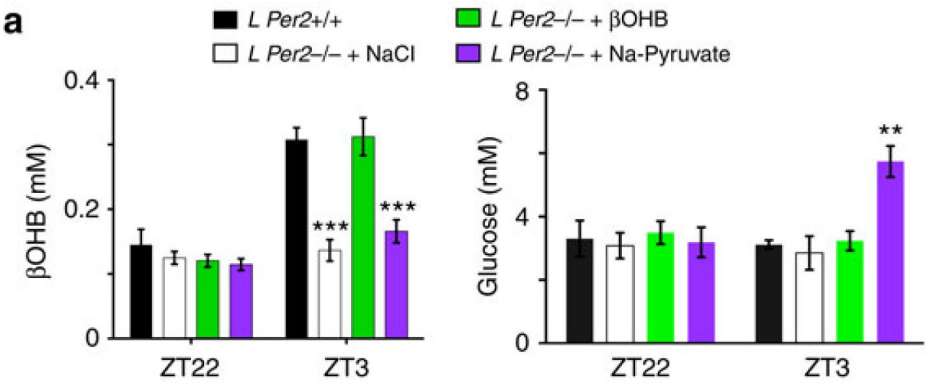


Figure 1 (Figure 4a in Full Article) **Rescue of food anticipation in L Per2$^{-/-}$mice by ß-hydroxybutyrate**. (a) Timed release of ßOHB (green) but not NaCl (white) or Na-Pyruvate (purple) in L Per2$^{-/-}$ mice mimics the ßOHB levels in plasma of L Per2$^{+/+}$ control animals (black). Measured after 15 days of infusion. Figure reproduced from Chavan et al. in Nature Communications as reference previously.

Purpose of the study:

Researchers were interested to know where Food Anticipation (FA) signals originate and what role components of the circadian clock might play. To test the potential of ßOHB as FA signal, iPRECIO SMP-300 programmable minimpumps were used to release ßOHB s.c. 6 hours prior to meal time under Restricted Feeding (RF) at ZT22 to reach a concentration normally observed in WT mice under RF preceeding feeding time.

iPRECIO SMP-300 pumps were used to test the potential of ßOHB as a FA signal.

Short methods or use of the pumps:
iPRECIO SMP-300 pumps were programmed to infuse saline vehicle at 2 ul/h, or D-ßOHB at 2 ul/h, or Sodium pyruvate at 5 ul/h, or coconut oil at 5 ul/h prior to meal time (6 h, ZT22-ZT4) under Restricted Feeding (RF)

Results/significance:
Liver-derived ketone bodies are necessary for food anticipation.
Timed Release of ßOHB partially rescues FA.

Research Need:
Timed Release of ßOHB in free moving animal with minimum or no handling to reduce stress and any confounding effects.

Additional information on mini-pump implant
Male and female L Per2$^{+/+}$ and L Per2$^{-/-}$ mice (3-5 months old)Telemetry transmitter (G2 E-mitter) was i.p. implanted in each mouse under gaseous anaesthesia. At least 10 days after the transmitter implantation an iPRECIO programmable micro infusion pump (SMP/UCD 300; Primetech Corp., Japan) was implanted in subgluteal space(s.c. administration) on the back of each L Per2$^{-/-}$ mouse. Subcutaneous administration.

Related Circadian rhythm Research using iPRECIO SMP-200 in mice
In vivo imaging of clock gene expression in multiple tissues of freely moving mice
Nature Communications 7, Article number: 11705 doi:10.1038/ncomms11705
https://www.nature.com/articles/ncomms11705

Research Applications 2

SC Administration

Can different dosing (12 hour rectangular exposure profile) and terminating profile (a slow-step down) of Nicotinic Acid (NiAc) prevent/delay tolerance development and attenuate the FFA rebound development respectively.

Tobias Kroon (2016) PhD Thesis,
<Optimizing Nicotinic Acid Delivery for Durable Anti-lipolysis and Improved Metabolic Control>,
http://pub.epsilon.slu.se/13324/
http://pub.epsilon.slu.se/13324/1/kroon_t_160429.pdf
Thesis and publications cover Drug Discovery implications
1. Importance of time-series disease model
2. Continuous vs. intermittent drug exposures /Programmable, implantable mini-pump
3. Time exposure to physiology/Shape of exposure
4. Meta-analysis/Rank candidates/Predict designs

Tobias Kroon, Ann Kjellstedt, Pia Thalén, Johan Gabrielsson, Nicholas D. Oakes
Dosing Profile Profoundly Influences Nicotinic Acid's Ability to Improve Metabolic Control in Rats
The Journal of Lipid Research, doi: 10.1194/jlr.M058149 , July 13, 2015
https://www.jlr.org/article/S0022-2275(20)35497-3/fulltext

Kroon T, Baccega T2, Olsén A, Gabrielsson J, Oakes ND
Nicotinic acid timed to feeding reverses tissue lipid accumulation and improves glucose control in obese Zucker rats [S].
J Lipid Res. 2017 Jan; 58 (1): 31-41 Doi: 10.1194 / jlr.M 068395. Epub 2016 Nov 15.
https://www.ncbi.nlm.nih.gov/pubmed/27875257

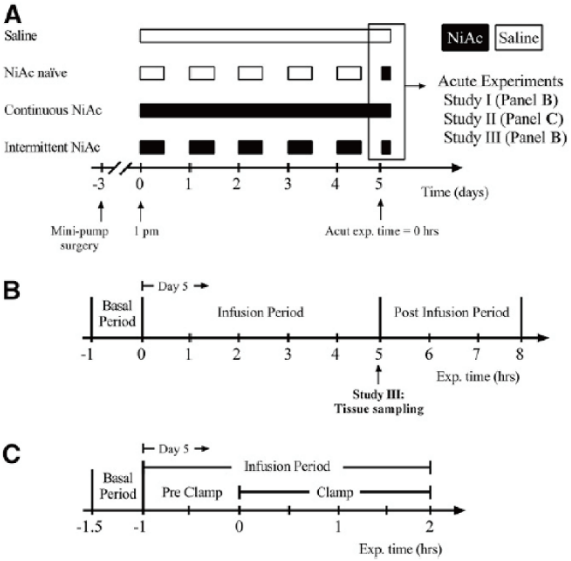


Fig. 2 (Figure 1 in Kroon et al.)
A: NiAc and saline infusion profiles across studies I–III.
Black (NiAc) and open (saline) bars represent time periods of constant rate infusions during days 1–5. B: Terminal protocol for studies I (NiAc-induced FFA lowering) and III (NiAc-induced changes in adipose tissue gene expression).
C: Terminal protocol for study II (hyperinsulinemic-isoglycemicla clamps).

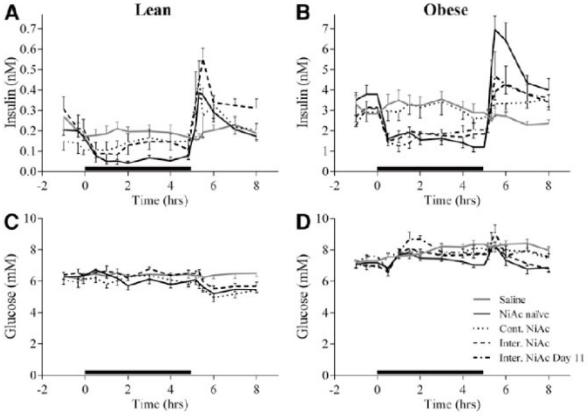


Fig. 3. (Figure 5 in Kroon et al.) Plasma insulin (A, B) and glucose (C, D) concentration in lean (left) and obese (right) following infusion of saline (lean n = 5, obese n = 12) or NiAc (0.17µmol·min -1·kg -1) given acutely (NiAc naïve, n = 7/group) or following 5 days continuous (Cont. NiAc, lean n = 4, obese n = 8) or intermittent (Inter. NiAc, lean n = 4, obese n = 9) or 11 days intermittent (Inter. NiAc Day 11, obese n = 4) dosing. The black horizontal bar represents the period of acute NiAc/saline infusion. Data presented as mean ± SE.

Purpose of the study:

Dosing Profile Profoundly Influences Nicotinic Acid's Ability to Improve Metabolic Control in Rats

Researchers wanted to compare the ability of continuous versus intermittent NiAc administration to suppress FFA levels in metabolic healthy and insulin-resistant rats.

The abruptness of terminating nicotinic acid delivery has a profound effect on free fatty acid and insulin rebound in rats

The aim of this study was to determine whether a slow step-down NiAc infusion protocol (Step-Down group) vs. simply turning infusion off (On/Off group) could attenuate the FFA rebound development.

iPRECIO SMP-200 pumps were programmed to deliver the required exposure profiles of Nicotinic Acid to study impact on tolerance development (see figure 2A) and attenuate the FFA rebound development respectively (not shown)

Results/significance:

An Intermittent NicAc dosing strategy succeeded in retaining FFA lowering and improving insulin sensitivity in obese Zucker rats. Gradual step-down reduction of NiAc infusion actually degraded the anti-lipolytic effectiveness of NiAc compared to abrupt withdrawal.

Research Need:

Ability to quickly and easily adjust dosing profiles based on PK and PD effects and deliver doses without stressors which could change metabolic activity of animals.

Research Applications 3

Intrathecal Administration

Continuous infusion of PKA and ATP at 1µl/hour for 14 days where solution in pump was changed every 2 days due to stability of PKA and ATP.

Kenji Suehiro, Yuka Nakamura, Shuai Xu, Youichi Uda, Takafumi Matsumura, Yoshiaki Yamaguchi, Hitoshi Okamura, Toshihide Yamashita & Yoshinori Takei

Ecto-domain phosphorylation promotes functional recovery from spinal cord injury

Scientific Reports 4 , Article number: 4972 (2014) doi:10.1038/srep04972

http://www.nature.com/articles/srep04972

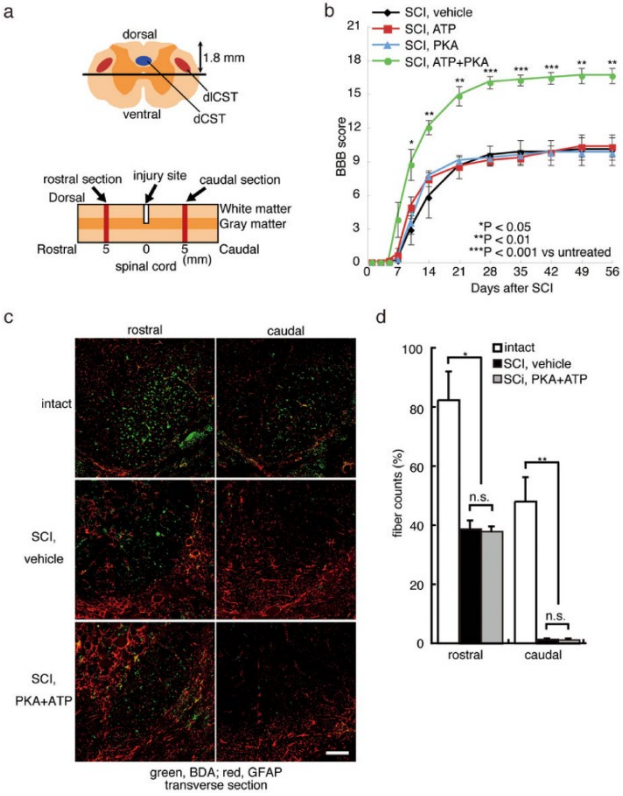


Figure 4 is reproduced from Ecto-domain phosphorylation promotes functional recovery from spinal cord injury http://www.nature.com/articles/srep04972 under Creative Common Attribution 4.0 International (CC BY 4.0) http://creativecommons.org/licenses/by/4.0/.
No changes were made for reproduction from Fig. 1 of Suehiro et al.

Figure 4 (Figure 1 from Suehiro et al)
| Treatment with PKA plus ATP diminishes damage from traumatic SCI. (a) The depth of injury and location of sections used in (c) are illustrated schematically. The dorsal corticospinal tract (dCST) and the dorsolateral corticospinal tract (dlCST) were severed. (b) The BBB scores of vehicle-treated, PKA-treated, ATP-treated and PKA1ATP-treated SCI rats were assessed at the indicated days after SCI. The points on the graph indicate the average BBB score from six independent rats, and the error bars indicate the standard deviation (S.D.) (*p , 0.05, **p , 0.01, ***p , 0.001 vs.vehicle-treated rats, Student's t-test). (c) The BDA-labelled dCST was visualised. Images are taken from transverse sections at either 5 mm caudal or rostral to the lesion, as shown in (a). The bar indicates 25 mm. (d) The number of BDA-positive axons at T8 or T10 was normalised to the number of BDA positive axons at C1 (intact region of the spinal cord). The average and the S.D. from three independent animals are shown. No significant differences between the vehicle-treated rats and the PKA/ATP-treated rats were observed (*p , 0.05, **p , 0.01,

Purpose of the study:
Investigate if inhibition of Nogo-66 receptor (NgR) via ecto-domain phosphorylation by protein kinase A (PKA), which blocks activation of the receptor can promote recovery following spinal cord injury.

iPRECIO SMP-200 pumps were used to infuse PKA plus ATP for 14 days at 1µl/hour. Solution in reservoir was changed every 2 days.

Results/significance:
Authors found that infusion of PKA plus ATP into the damaged spinal cord can promote recovery of locomotor function.

Research Need:
Ability to replace unstable test articles or drugs easily and rapidly without additional surgeries and stress.

Related publication examples: Refilling to Improve Test Article Stability

Hemoglobin induced lung vascular oxidation, inflammation, and remodeling contributes to the progression of hypoxic pulmonary hypertension and is attenuated in rats with repeat dose haptoglobin administration
Free Radical Biology and Medicine D Irwin et al.doi:10.1016/j.freeradbiomed.2015.01.012
http://www.sciencedirect.com/science/article/pii/S0891584915000192

Free hemoglobin induction of pulmonary vascular disease: evidence for an inflammatory mechanism.
Am J Physiol Lung Cell Mol Physiol. 2012 Aug;303(4):L312-26. Epub 2012 Jun 22.
http://www.ncbi.nlm.nih.gov/pubmed/22728465

Research Applications 4

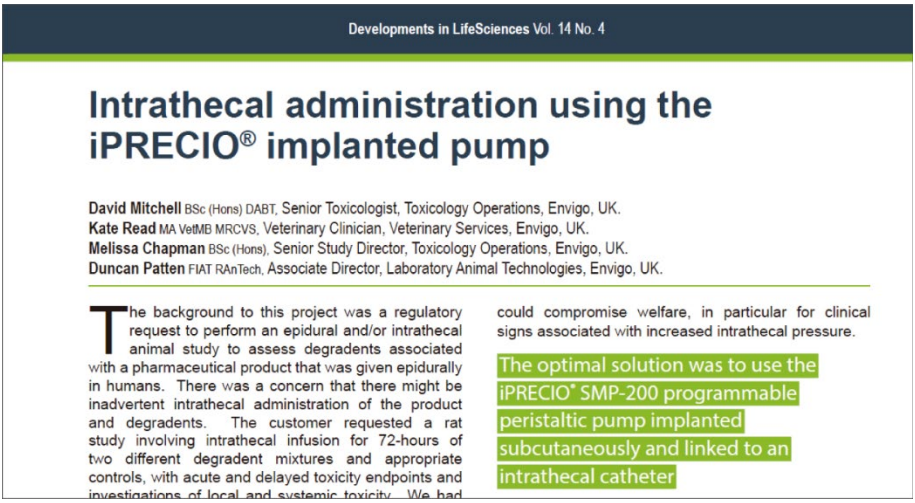
Intrathecal Administration

Excerpt from Mitchell et al. Full reference in box.

Regulatory request to perform an epidural and/or intrathecal animal study to assess degradents associated with a pharmaceutical product that was given epidurally in humans.

Mitchell D., Read, K., Chapman M. and Patten D.
Intrathecal administration using the iPRECIO® implanted pump
Development in Life Sciences, Vol 14, No. 4
https://doc.primetech.co.jp/hubfs/iPRECIO/Envigo_Pharma_Dils_14.4.4_(intrathecal-recathco).pdf

Purpose of the study:
The customer requested a rat study involving intrathecal infusion for 72-hours of two different degradent mixtures and appropriate controls with acute and delayed endpoints and investigations of local and systemic toxicity. Clinical relevant concentrations of degradents to attain comparable exposure with humans would be necessary.



Developments in LifeSciences Vol. 14 No. 4

Intrathecal administration using the iPRECIO® implanted pump

David Mitchell BSc (Hons) DABT, Senior Toxicologist, Toxicology Operations, Envigo, UK.
Kate Read MA VetMB MRCVS, Veterinary Clinician, Veterinary Services, Envigo, UK.
Melissa Chapman BSc (Hons), Senior Study Director, Toxicology Operations, Envigo, UK.
Duncan Patten FIAT RAnTech, Associate Director, Laboratory Animal Technologies, Envigo, UK.

The background to this project was a regulatory request to perform an epidural and/or intrathecal animal study to assess degradents associated with a pharmaceutical product that was given epidurally in humans. There was a concern that there might be inadvertent intrathecal administration of the product and degradents. The customer requested a rat study involving intrathecal infusion for 72-hours of two different degradent mixtures and appropriate controls, with acute and delayed toxicity endpoints and investigations of local and systemic toxicity. We had could compromise welfare, in particular for clinical signs associated with increased intrathecal pressure.

The optimal solution was to use the iPRECIO® SMP-200 programmable peristaltic pump implanted subcutaneously and linked to an intrathecal catheter

iPRECIO SMP-200 pumps were used to infuse 1µl/hr of artificial CSF intrathecally following surgery and during the recovery period. Animals recovered well with no adverse clinical signs in the post –operative period. During the treatment period; infusion at 30µl/hr, a small number of animals (5 out of 72) showed hindlimb paresis. Examination of aspirated dose volumes demonstrated accurate pump function.

Results/significance

This method (iPRECIO SMP-200 linked to an intrathecal catheter) is suitable for controlled continuous infusion into the intrathecal space of the rat. The surgical procedure is reproducible and considered to be less invasive than intrathecal access via the cisterna magna. The use of the programmable iPRECIO® pump allows for an ambulatory infusion model without the need to tether the animals. This permits behavioural assessment and is an improvement in animal welfare; animals are able to display normal behaviours post operatively.

Research Need:

A standard method for intrathecal infusion in industry and academia which would not be a confounding factor in the assessment of CNS endpoints (modified Irwin assessment).
The infusion system must provide a suitable flow rate over at least 72 hours.

- The pump must allow the flexibility to start infusion immediately following surgery or at a later time.
- The pump must have a reservoir that can be evacuated and refilled, percutaneously, by syringe and needle so there would be the opportunity for a period of recovery from surgery before administration of the degradant mixtures while avoiding the risk of catheter occlusion by administering saline or artificial cerebrospinal fluid.

Research Applications 5

Jugular Vein (IV) Administration

Aldosterone was continuously infused with SMP-200 programmable infusion pump that delivered aldosterone into the jugular vein. D-Aldosterone was infused into the jugular vein at a dose of 30 $\mu g \cdot kg^{-1} \cdot day^{-1}$ in a solution of 15% ethanol,
50% DMSO, and 35% water at a concentration of 10 mg aldosterone/ml.

Enhanced Resistance to Permeability Transition in Interfibrillar Cardiac Mitochondria in Dogs: Effects of Aging and Long Term Aldosterone Infusion.
Am J Physiol Heart Circ Physiol ajpheart.00674.2012;
https://pubmed.ncbi.nlm.nih.gov/23241318/

Purpose of the study:
Effect of aging and long-term aldosterone infusion on respiratory function and resistance to mitochondrial permeability transition (MPT) in subsarcolemmal and interfibrillar cardiac mitochondria (SSM and IFM) from healthy young (1 year) and old (8 year) female beagles.

iPRECIO SMP-200 pumps were used to infuse Aldosterone for 14 weeks at a dose of 30 $\mu g \cdot kg^{-1} \cdot day^{-1}$ The pump reservoir was 900 µl and was refilled percutaneously every 20–30 days through an injection port on the pump. The pump reservoir was evacuated before refilling to ensure the pump had properly discharged its contents and was then refilled using a 26-gauge needle. This procedure was done in conscious animals with no evidence of discomfort.

Results/significance
Authors demonstrated in a large animal model that resistance to MPT is greater in IFM than in SSM in young and old female dogs. When old dogs were stressed with aldosterone infusion, there was selective enlargement of SSM and greater susceptibility to MPT, with no change to IFM.

Research Need:
Long term/chronic 14 week infusions with the ability to refill and check performance of implanted pumps.

Research Applications 6

Brain Administration

Pumps were programmed to instant mode, constant mode and 5µl/hour infusion rate. They were initially loaded with isotone saline or 0.1 mM MTX. Two days later, residual saline or MTX was extracted from the pump reservoirs and refilled with 960µl of 0.3 µg/ml ^{125}I-UdR or ^{127}I-UdR. See figure 6 below for results obtained. Reproduced with permission from Thisgaard et al. (CC BY-NC-ND 4.0).

Thisgaard et al.
Highly Effective Auger-Electron Therapy in an Orthotopic Glioblastoma Xenograft Model using Convection-Enhanced DeliverHighly Effective Auger-Electron Therapy in an Orthotopic Glioblastoma Xenograft Model using Convection-Enhanced Deliver
Theranostics 2016, Vol. 6, Issue 12 2016; 6(12): 2278-2291. doi: 10.7150/thno.15898
http://www.thno.org/v06p2278.htm

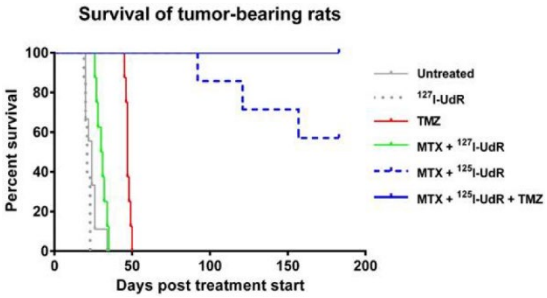


Figure 6. Kaplan-Meier plot showing that the survival benefit of neoadjuvant MTX + ^{125}I-UdR as stand-alone Auger-therapy (group4) or with concomitant, systemic TMZ chemotherapy (group5) was highly significant compared with the non-radioactive, but chemically identical treatment MTX + ^{127}I-UdR (group3, p=0.0001 and p<0.0001, respectively) or untreated controls (group1, both p<0.0001). The Auger-therapy was also significantly better than systemic TMZ-chemotherapy alone (group6, p=0.0001). Reproduced with permission from Thisgaard et al. (CC BY-NC-ND 4.0).

Purpose of the study:

The overall aim of this was to test the effect and safety profile of ^{125}I-UdR therapy in vitro and in vivo on immature Glioblastomas (GBMs) spheroid cultures (GSCs) and orthotopic xenografted GBM-bearing rats, respectively. A further objective was to determine if further therapeutic effect was achieved when combining ^{125}I-UdR therapy with the currently used first-line chemotherapeutic agent TMZ.

Pumps were initially loaded with isotone saline or 0.1 mM MTX. Two days later, residual saline or MTX was extracted from the pump reservoirs and refilled with 960µl of 0.3 µg/ml ^{125}I-UdR or ^{127}I-UdR.

Results/significance:

The multidrug approach including CED of MTX and the AEE-compound ^{125}I-UdR in combination with systematic TMZ was safe and very effective in the orthotopic xenograft GBM model, leading to 100% survival.

Research Need:

The ability to evaluate combinational therapy/multidrug approach easily and rapidly without additional surgeries and stress.

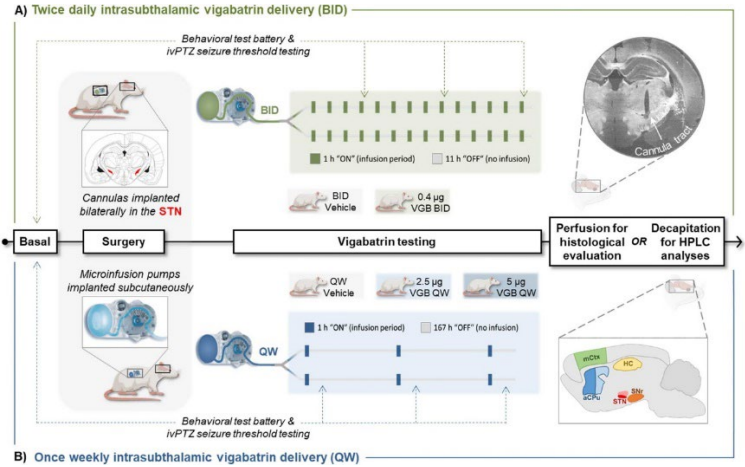
Research Applications 7

Brain Administration

”Pumps were programmed to run with a flow rate of 0.2 µL/h for 1 h at the time of cannula implantation to avoid cannula blockage during implantation. Pumps subsequently ran for the duration of the drug testing period following one of two drug application regimens: (1) 1 h “on”, 11 h “off”, for twice daily (bis in die, BID) drug infusion of 0.4 µg VGB, or (2) 1 h “on”, 167 h “off”, for once weekly (quaque week, QW) drug infusion of 2.5 or 5 µg VGB. ” See Figure 1 below.

Devlin MacKeigan et al.
Chronic intermittent convection-enhanced delivery of vigabatrin to the bilateral subthalamic nucleus in an acute rat seizure model. [Open Access]
Epilepsy Research 199 (2024): 107276.
https://www.sciencedirect.com/science/article/pii/S0920121123002012

Keywords: Basal ganglia Epilepsy GABA transaminase Intracerebral pharmacotherapy Pentylenetetrazole Tolerance



Purpose of the study:

”The purpose of the study was to investigate the antiseizure effects of chronic intermittent intra-subthalamic nucleus (STN) convection-enhanced delivery of vigabatrin (VGB) in an acute rat seizure model, with the aim of circumventing tolerance development and preventing adverse effects associated with continuous intracerebral pharmacotherapy.”

Results/significance:

”Intermittent CED of VGB to the bilateral STN was found to have antiseizure effects and to be well tolerated. Our data indicate improved efficacy and adverse effect profile compared to continuous intra-STN VGB delivery (Gey et al., 2016).”

Research Need:

”The study highlights the need for further research into optimizing drug delivery regimens to enhance long-term seizure control with minimal adverse effects.”

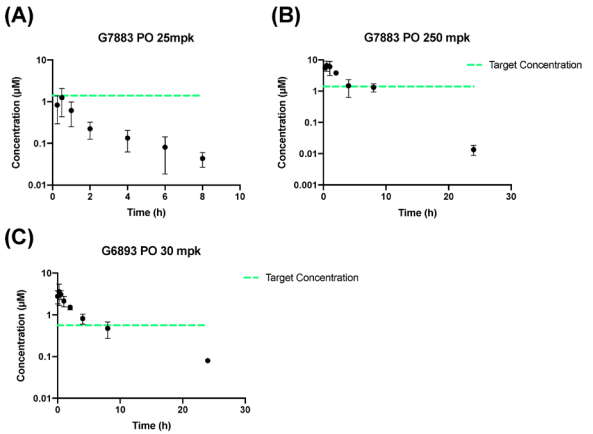
Research Applications 8

IV and SC Administration

Formulations selected for G7883 in the iPRECIO pump IV infusion study were 20% Dimethyl Sulfoxide (DMSO): 80% Polyethylene glycol 400 (PEG400) at 3.3 mg/mL. Five female C57BL-6 mice were dosed at 0.8 mg/kg/h with an infusion rate of 0.2 mL/h/kg (5 uL/h). The pump was refilled every 24 h with a study duration of 7 days. The formulation selected for G6893 in the iPRECIO pump IV infusion study was 100% PEG400 at pH 6 at 2.5 mg/mL. Three female C57BL-6 mice with a body weight ranging from 17 to 18 g were dosed at 0.5 mg/kg/h with an infusion rate of 0.2 mL/h/kg (5 µL/h). The pump was refilled every 24 h with a study duration of 5 days.

An, Le, et al.
Early Stage Preclinical Formulation Strategies to Alter the Pharmacokinetic Profile of Two Small Molecule Therapeutics. [Open Access]
Epilepsy Research 199 (2024): 107276.
Pharmaceuticals 17.2 (2024): 179. https://www.mdpi.com/1424-8247/17/2/179

Keywords: drug delivery; PO; IV infusion; IP; SC; small molecule; PK profile; exposure



Purpose of the study:

The study aimed to investigate formulation strategies to enhance the pharmacokinetic (PK) profiles of two anti-cancer agents, G7883 and G6893.

Results/significance:

The study found that various formulation and delivery strategies significantly improved the PK profiles of G7883 and G6893:

Research Need:

The study highlights the need for innovative formulation strategies and delivery methods to optimize the PK profiles of therapeutic compounds.

Research Applications 9

SC Administration

Corticosterone Pumps

Pumps were programmed in 24 h repetitive loops to deliver corticosterone at 4 µL/h from ZT6-ZT10, 6 µL/h from ZT10-16, 4 µL/h from ZT16-ZT18 and a maintenance dose of 1 µL/h to avoid clotting in the outlet tubing for the remaining 12 h, ZT18-ZT6.

Bering, Tenna, et al.
Circadian Clock Genes Are Regulated by Rhythmic Corticosterone at Physiological Levels in the Rat Hippocampus.
Epilepsy Research 199 (2024): 107276.
Neuroendocrinology 113.10 (2023): 1076-1090. https://karger.com/nen/article/113/10/1076/860659

Keywords: Clock gene, Corticosterone, Hippocampus, Programmable pumps, Suprachiasmatic nucleus

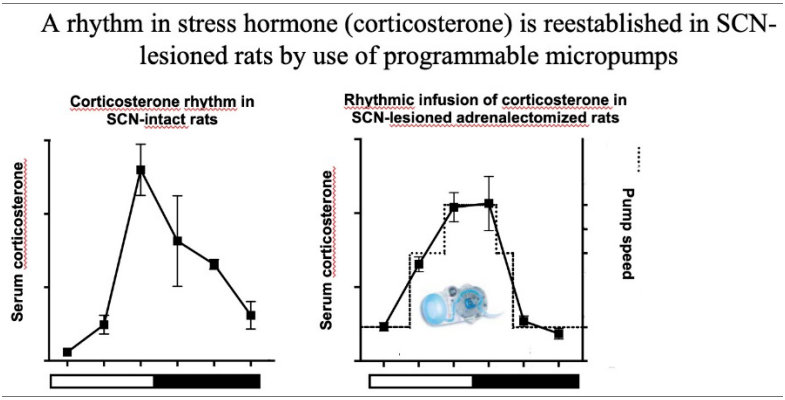


Figure kindly provided by Dr. T Bering.

Purpose:
We examined how physiological corticosterone rhythms affect clock gene expression by replicating endogenous daily oscillations.

Results:
We examined how physiological corticosterone rhythms affect clock gene expression by replicating endogenous daily oscillations.

Conclusion:
Rhythmic corticosterone drives hippocampal clock gene rhythms, suggesting SCN regulates the hippocampal circadian oscillator by controlling circulating glucocorticoid rhythms.

Related:

Rhythmic Release of Corticosterone Induces Circadian Clock Gene Expression in the Cerebellum [Open Access] Neuroendocrinology. 2019 Sep 27. doi: 10.1159/000503720
https://www.karger.com/Article/Abstract/503720
Keywords: Cerebellum, Circadian, Clock gene, Corticosterone, Suprachiasmatic nucleus,iPRECIO programmable micropump

Research Applications 10 & 11 Pump Highlights

SC Administration & NHP

Identical infusion protocols used for both studies. iPRECIO SMP-200, with 15 IU/kg human follicle-stimulating hormone was embedded subcutaneously under anesthesia and injected 7 µl/hr for 10 days. Continuous infusion for 10 days.

Moghe, P., Belousov, R., Ichikawa, T. et al.
Coupling of cell shape, matrix and tissue dynamics ensures embryonic patterning robustness.
Nat Cell Biol 27, 408–423 (2025). https://www.nature.com/articles/s41556-025-01618-9 [Open Access]
Subjects: Embryogenesis, Morphogenesis, Pattern formation

Nakaya, M., Iwatani, C., Tsukiyama-Fujii, S. et al.
Non-viral generation of transgenic non-human primates via the piggyBac transposon system.
Nat Commun 16, 2179 (2025). https://www.nature.com/articles/s41467-025-57365-w [Open Access]
Subjects: Disease model, Genetic engineering, Genetic vectors, Transgenic organisms

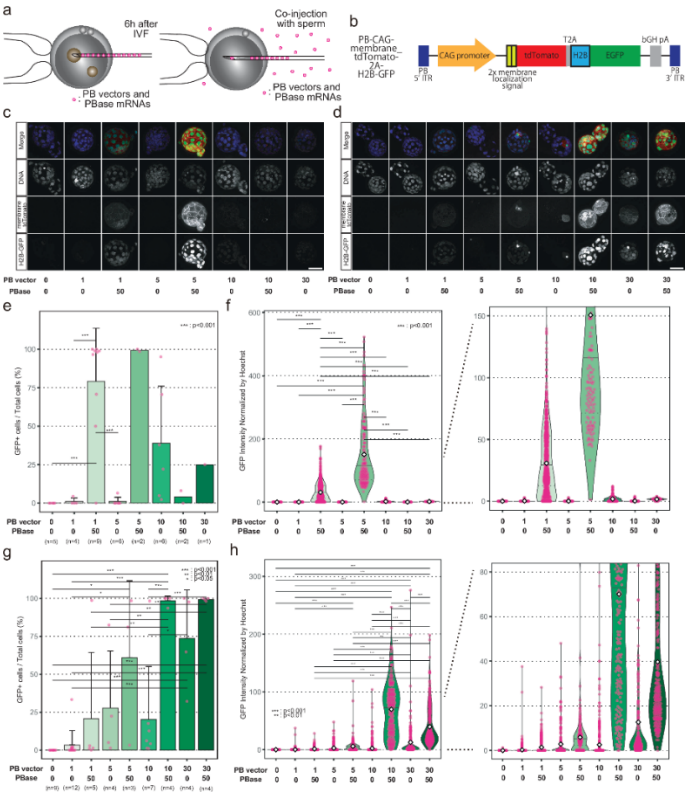


Fig. 1
from Nakaya et al. | Identification of the optimized conditions for piggyBac co-injection in mice.

Disease Induction: Sustained ICV delivery of pathogenic autoantibodies (#003-102 Ab) at 10 µg/h (2.0 µL/h) induced robust behavioral abnormalities mirroring human symptoms.

Therapeutic Intervention: Concurrent ICV infusion of ART5803 at 2.0 µL/h reversed neurological deficits within 2 weeks, highlighting rapid therapeutic potential.

Kanno, A., Kito, T., Maeda, M. *et al.* **Monoclonal humanized monovalent antibody blocking therapy for anti-NMDA receptor encephalitis.**

Nat Commun 16, 5292 (2025).

https://www.nature.com/articles/s41467-025-60628-1

[Open Access]

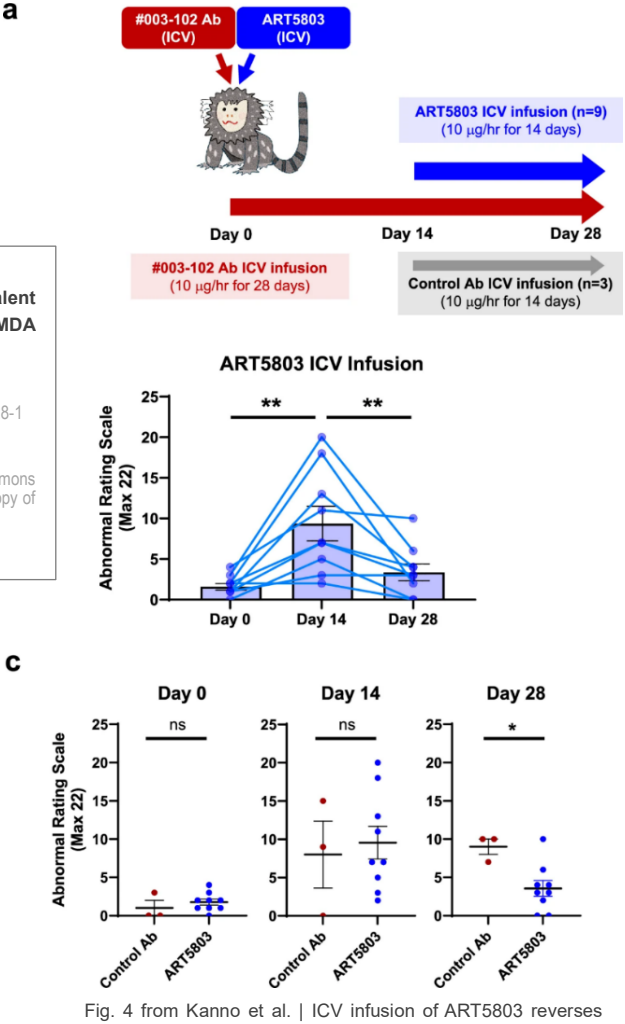


Fig. 4 from Kanno et al. | ICV infusion of ART5803 reverses abnormal behaviors induced by pathogenic autoantibody (#003-102 Ab) in marmoset disease model.

See also. Arialys Therapeutics Publishes Preclinical Data & Clinical Trial Initiated

Research Applications 13 Pump Highlights

SC Administration & Rats

After recovery, pumps infused saline for 5 days, the last 3 of which were used as baseline sleep recordings. Following saline infusions, pumps delivered escalating-dose oxycodone twice a day (ZT0-2 and ZT12-14) for 14 days (0.5–8.0 mg/kg/inf, 2 inf/d), resulting in 28 total infusions. Starting with 0.5 mg/kg, rats received the following: number of infusions at oxycodone dose: 4 at 0.5, 6 at 1.0, 6 at 2.0, 6 at 4.0, 6 at 8.0. The last infusion (8.0 mg/kg) occurred from ZT0-2 on withdrawal day 1 (W1).

Gulledge, M., Carlezon Jr, W. A., McHugh, R. K., Kinard, E. A., Prerau, M. J., & Chartoff, E. H. (2025).
Spontaneous oxycodone withdrawal disrupts sleep, diurnal, and electrophysiological dynamics in rats.
PloS one, *20*(1), e0312794. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0312794 [Open Access]

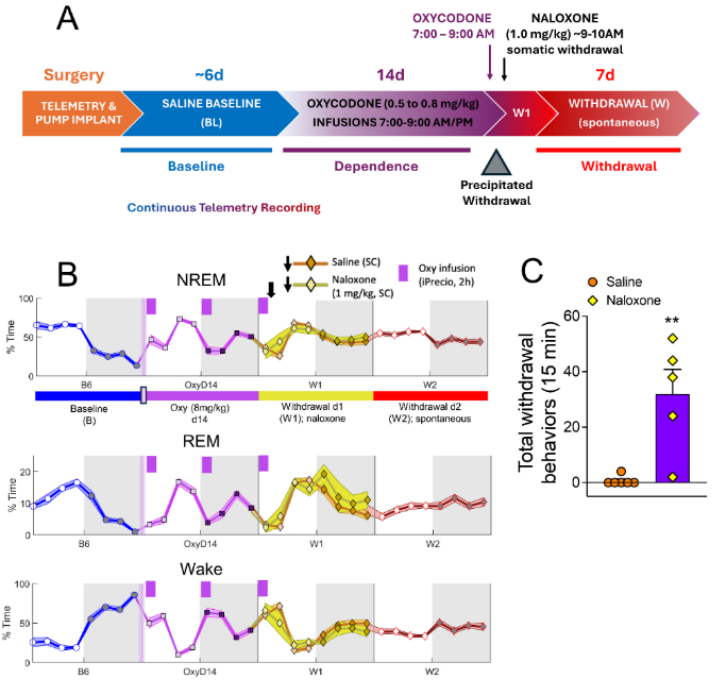
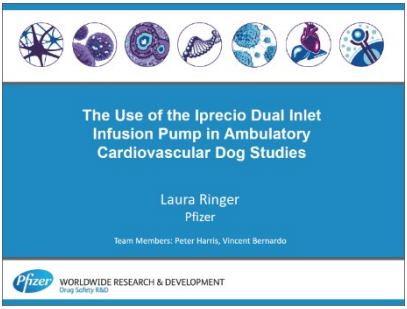


Fig. 1 from Gulledge et al. Escalating oxycodone dose infusion protocol modulates sleep stages and produces dependence in male rats.

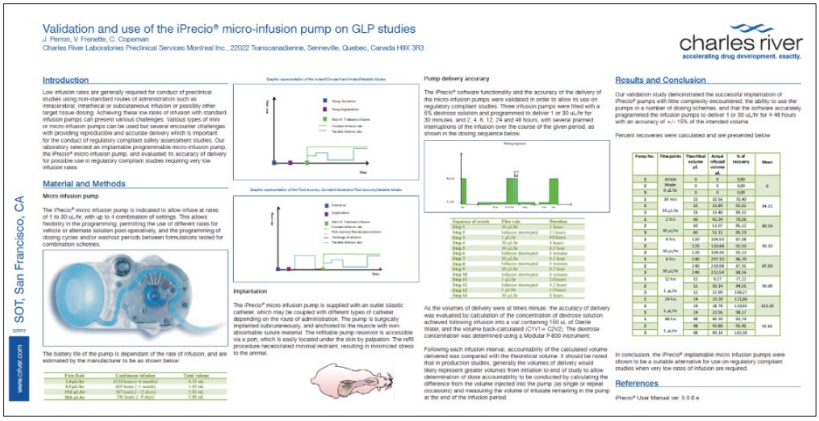
GLP Studies with iPRECIO Pumps



Laura Ringer
The use of the iPRECIO Dual Inlet Infusion Pump in Ambulatory Cardiovascular Dog Studies
DSI East Coast User Group Meeting, Philadelphia, PA, United States October 29th and 30th 2015

Duncan Patten (Huntingdon Life Sciences, UK)
Use of iPRECIO implantable micro infusion pumps in rats
4th Infusion Technology Organization Meeting, May 8th-9th 2014, Harrogate, UK.

Perron J., Frenette V., and Copeman C.
Validation and use of the iPRECIO® Micro Infusion Pump on GLP studies
Society of Toxicology Annual Meeting, San Francisco, United States, March 11th to 14th 2012.



Toxicology Studies with iPRECIO Pumps

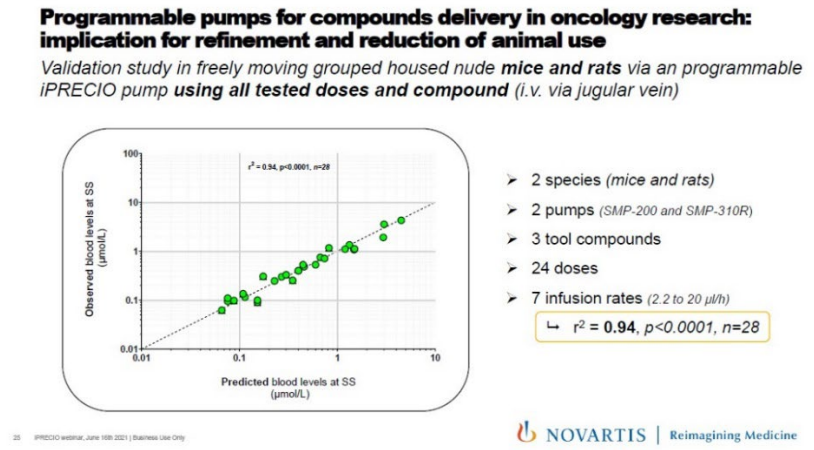
Masaru Tsuboi,Yoshihide Ueda,Yasufumi Ota,Hiroshi Takehara,Takuya Aoshima, Fukutaro Mizuhashi
Physiological conditions in iPRECIO® -implanted rats
Fundamental Toxicological Sciences Vol.3 (2016) No.1 p.1-8
https://www.jstage.jst.go.jp/article/fts/3/1/3_1/_article

Webinar

Webinar: Compound Delivery, PK-PD & Validation Studies in Oncology Studies

Christian Schnell, Associate Director Oncology NIBR Novartis in Basel

https://insidescientific.com/webinar/programmable-pumps-for-compound-delivery-in-oncology-research/



During this on-demand webinar, Christian Schnell describes the validation studies performed in his pharmacology unit in rats and mice. Accurate PK-PD assessment and corresponding antitumor activity were assessed among several drug discovery programs.

Presentation Highlights:

- Traditional methods used for developing PK/PD models (4:00)
- PK/PD models and the limitations of traditional dosing methods (6:33)
- Methods and benefits of implantable microinfusion pumps in both rats and mice (12:36)
- Validation studies using implantable pumps (17:41)
- Experimental application of implantable pumps (24:36)
- The use of implantable pumps to assess TI (28:18)
- Potential future applications and considerations (36:05)

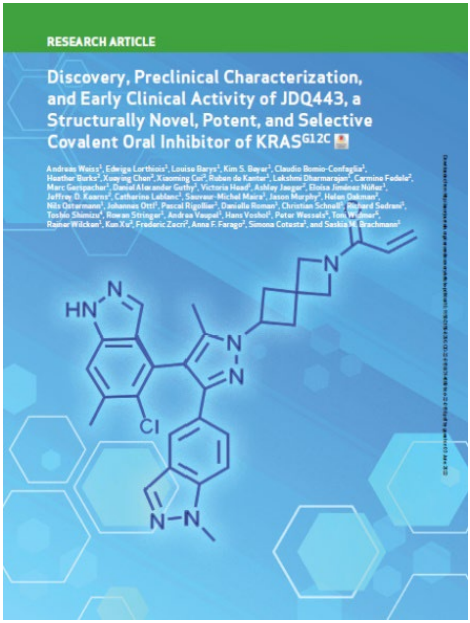
Related Reference.

Weiss, Andreas, et al. "Discovery, Preclinical Characterization, and Early Clinical Activity of JDQ443, a Structurally Novel, Potent, and Selective Covalent Oral Inhibitor of KRASG12C." Cancer Discovery 12.6 (2022): 1500-1517.

- iPRECIO SMP-310R Programmable pumps were used to better understand the relationship between PK, target occupancy, and efficacy.
- Continuous infusion demonstrated that Daily AUC rather than Cmax or Time-over-threshold as the driver of efficacy of TDQ443.

Weiss, Andreas, et al. **"Discovery, Preclinical Characterization, and Early Clinical Activity of JDQ443, a Structurally Novel, Potent, and Selective Covalent Oral Inhibitor of KRAS^{G12C}."**
Cancer Discovery 12.6 (2022): 1500-1517. https://doi.org/10.1158/2159-8290.CD-22-0158 [Open Access]

“To assess the effect of continuous dosing on tumor growth, LU99 tumor–bearing nude mice were implanted subcutaneously with a programmable microinfusion pump (iPRECIO, SMP310R, Primetech Corporation) as previously described (56). For this purpose, the catheter connected to the microinfusion pump was inserted into the left external jugular vein via midcervical incision, and the body of the microinfusion pump was implanted subcutaneously on the flank of the mice opposite to the xenograft tumor. For infusion, JDQ443 was dissolved in 30% PEG and 10% Kolliphor at a concentration of 3 and 10 mg/mL. The infusion rate of 4 µL/h was programmed with iPRECIO Management Software v1.0.4.0. Pumps were refilled with vehicle or JDQ443 daily. At days 2 to 3, 9 to 10, and 12 to 13, the drug released was quantified in blood samples collected at the tail vein by LC-MS/MS. “



Webinars with iPRECIO Pump use. “(1) The best solution is to get rid of stress because training is not really a solution. (2) An implantable pump is the only way to deliver the compound without interfering at the moment of delivery.”.

WE 1 Schnell: Gold Standard Physiological Measurements and Novel Drug Delivery Methods: Quality Data in Mice to Marmosets. Christian Schnell, Associate Director Oncology NIBR Novartis in Basel

https://insidescientific.com/webinar/gold-standard-physiological-measurements-and-novel-drug-delivery-methods-iprecio-pt1/

WE 2 Doyle: Gold Standard Physiological Measurements and Novel Drug Delivery Methods: Synthetic, Structural, and Mechanistic Investigations of Vitamin B12 Conjugates of the Anorectic Peptide PYY3-36 Dr Robert Doyle, The Laura J. and L. Douglas Meredith Professor of Biochemistry and Biotechnology, Syracuse University, Syracuse. https://insidescientific.com/webinar/gold-standard-physiological-measurements-and-novel-drug-delivery-methods-iprecio-pt2/

Henry, Kelly E., et al. "Vitamin B12 conjugation of peptide-YY3–36 decreases food intake compared to native peptide-YY3–36 upon subcutaneous administration in male rats." Endocrinology 156.5 (2015): 1739-1749. https://academic.oup.com/endo/article/156/5/1739/2422996?login=true

Register here for live and on-demand For more details, registration and access:

Live Oct. 7, 2025: Time: 8:00 AM (PST), 11:00 AM (EST) then available On-Demand.
Abstract Excerpt – First Paragraph and learning objectives.
Key preclinical studies in murine xenograft MM models demonstrated that continuous subcutaneous lenalidomide at 144 µg/day achieved superior tumor control (81% reduction in tumor volume) and prolonged time to treatment failure compared to standard daily bolus dosing, with no dose-limiting toxicities or significant hematologic suppression. Chronic dosing in healthy mice confirmed the absence of neutropenia, thrombocytopenia, or local tissue toxicity, supporting a favorable safety profile.

Dr Jamie Oliver, Chief Medical Officer, Starton Therapeutics
Learning Objectives:

- Understand the rationale and scientific basis for continuous low-dose lenalidomide delivery in hematologic malignancies, including the pharmacokinetic and pharmacodynamic advantages over conventional oral dosing.
- Evaluate preclinical and early clinical data supporting the efficacy and safety of STAR-LLD, and recognize the implications for patient outcomes and future therapeutic strategies.
- Identify the translational steps and regulatory considerations involved in advancing STAR-LLD from preclinical models to Phase 2 clinical trials.

This session is ideal for clinicians, researchers, and industry professionals interested in **drug delivery innovation**, myeloma therapeutics, and translational oncology.

iPRECIO Micro Infusion Pumps for Cancer Research

Solubility & Precipitation issues?

More difficult to dose correctly and need more control?

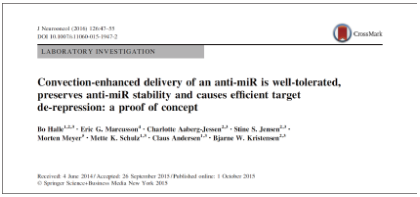
Program what you require

- Solubility issues and need a higher infusion flow-rate to reduce drug concentration and precipitation risk
- Difficult to dose correctly and need to be able to have accurate flow-rates/dose groups
- Suited for intermittent dosing of onco substances – daily for 1 hour or every 2 days for 2 hours.
- Would like to allow tumor size to grow to a certain size before drug infusion
- Want to program a drug holiday
- Want to evaluate chrono release for maximum efficacy and minimize toxicity

Cancer Research Publications

Establishment of an orthotopic bladder cancer model to evaluate continuous intravesical delivery of small molecule inhibitors in the nude rat
AACR 106th Annual Meeting 2015; April 18-22, 2015; Philadelphia, PA
http://cancerres.aacrjournals.org/content/75/15_Supplement/5146.short

Convection-enhanced delivery of an anti-miR is well-tolerated, preserves anti-miR stability and causes efficient target de-repression: a proof of concept.
Journal of Neuro-Oncology 2015 Oct 1.
http://link.springer.com/article/10.1007%2Fs11060-015-1947-2
http://www.ncbi.nlm.nih.gov/pubmed/26428358


J Neurooncol (2016) 126:47–55
DOI 10.1007/s11060-015-1947-2

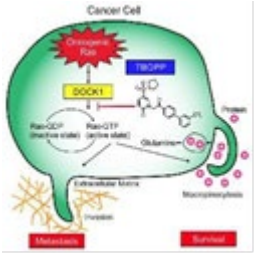
LABORATORY INVESTIGATION

Convection-enhanced delivery of an anti-miR is well-tolerated, preserves anti-miR stability and causes efficient target de-repression: a proof of concept

Bo Halle[1,2,3] · Eric G. Marcusson[1] · Charlotte Auberg-Jessen[2,3] · Stine S. Jensen[2,3] · Morten Meyer[2] · Mette K. Schaft[2,3] · Claus Andersen[2,3] · Bjarne W. Kristensen[2,3]

Received: 4 June 2014 / Accepted: 28 September 2015 / Published online: 1 October 2015
© Springer Science+Business Media New York 2015

Tajiri et al. (Kyushu University, Japan)
Targeting Ras-Driven Cancer Cell Survival and Invasion through Selective Inhibition of DOCK 1
Cell Reports 19, 969-980, May 2, 2017
http://dx.doi.org/10.1016/j.celrep.2017.04.016



Maxim Shevtsov et al.
Granzyme B Functionalized Nanoparticles Targeting Membrane Hsp70 - Positive Tumors for Multimodal Cancer Theranostics
Small, 2019 - Wiley Online Library
https://onlinelibrary.wiley.com/doi/abs/10.1002/smll.201900205

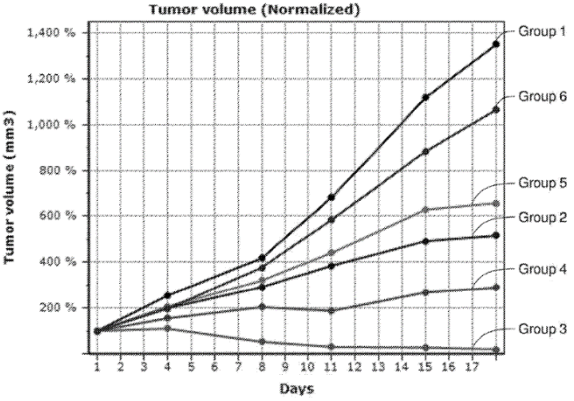
All things mouse with iPRECIO Programmable Pumps (IMS/SMP-300 and IMS/SMP-310R)

iPRECIO Micro Infusion Pumps for Cancer Research

US20200330445A1 Continuous delivery of lenalidomide and other immunomodulatory agents [Open Access]
Marina BOROVINSKAYA, Fotios PLAKOGIANNIS, Nisarg MODI, Tamanna LATHAR, Rod L. Hartwig, James C. OLIVER

See Example 1 https://patents.google.com/patent/US20220054473A1/en
Video (https://youtu.be/d8CHR7et5zs or https://www.linkedin.com/feed/update/urn:li:activity:6768444633161842688) from Start to 7 minutes. Rodent Studies of PK, Safety and Tolerability of LLD in Healthy and SCID Mice by Jamie Oliver Chief Medical Officer Starton Therapeutics.
Excerpts and Figure from **US20200330445A1** (SCID Mice 20 grams on average, Route of Administration (RoA) - SC)

"After the tumor reached an average size of 100-150 mm, iPrecio pump was surgically implanted into each of the mice . Dosing began twenty four hours post pump implantation. Each of Groups 3-6 was treated lenalidomide via continuous subcutaneous infusion at different hourly rate. The dosing lasted 14 days followed by one day off the treatment and lasted for another 14 days . The iPrecio pump was replaced after 14 days."



See Example 1
https://patents.google.com/patent/US20220054473A1/en

"This study unexpectedly showed that the continuous infusion route effectively reduced the tumor size in all animals treated at 6 mcg/hr while the intraperitoneal injection at a higher dose slowed progression but did not inhibit the growth of the tumor size. See FIG. 1. This study also showed that the continuous infusion route did not result in substantial loss of body weight or hematologic toxicity. See FIG. 2 and Table 1." From Borovinskya et al. US 2020/0330445 A1

The Ultimate Choice for Neuroscience

iPRECIO Micro Infusion Pumps for Drug Delivery
Implantable Programmable Refillable

- The only way to deliver compound without interfering at the moment of delivery
- Paired data sets: Program a recovery/baseline period prior to drug delivery for control period for comparison.
  - > Recovery period after surgery (pump stop or saline infusion)
  - > Baseline period (pump stop or saline infusion)
  - > Drug delivery /Treatment period (start pump or exchange from saline to drug)
    - Continuous
    - Intermittent
    - Dose escalation / de-escalation
    - Circadian
  - > Reversibility (pump stop or exchange to saline)
- Infuse directly to brain
- Infuse directly to intrathecal space
- SC, IP and IV administration

Example Drug Delivery Regimen (Figure 1 reproduced from Thisgaard et al. (CC BY-NC-ND 4.0)
Schedule what you require: program and/or exchange infusate as per study requirements

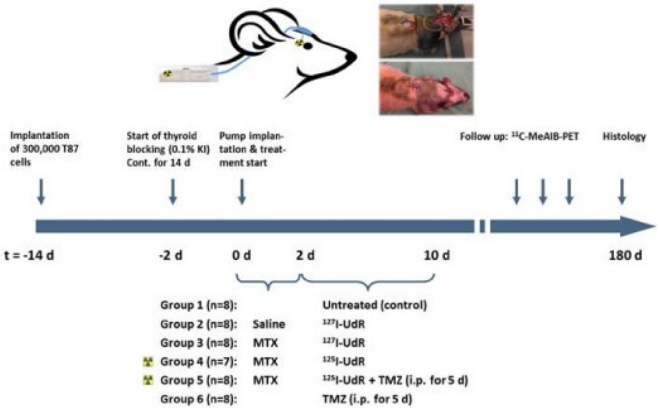


Figure 1 reproduced from Thisgaard et al. (CC BY-NC-ND 4.0)
Highly Effective Auger-Electron Therapy in an Orthotopic Glioblastoma Xenograft Model using Convection-Enhanced Delivery
Thisgaard et al. Theranostics 2016, Vol. 6, Issue 12 2016; 6(12): 2278-2291. doi: 10.7150/thno.15898

Selected CNS Publications

Intrastriatal Memantine Infusion Dampens Levodopa-Induced Dyskinesia and Motor Deficits in a Mouse Model of Hemiparkinsonism

BRIEF RESEARCH REPORT ARTICLE Front. Neurol., 05 December 2019

https://www.frontiersin.org/articles/10.3389/fneur.2019.01258/full

Key words: intracerebral brain infusion, levodopa-induced dyskinesia, memantine, N-methyl-D-aspartate receptor, Parkinson's disease

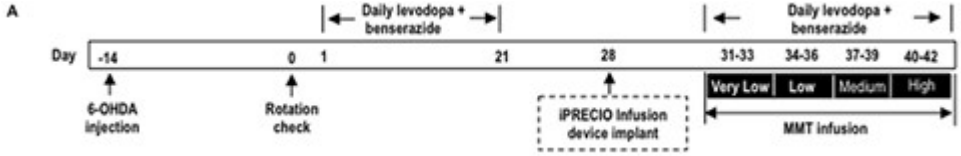


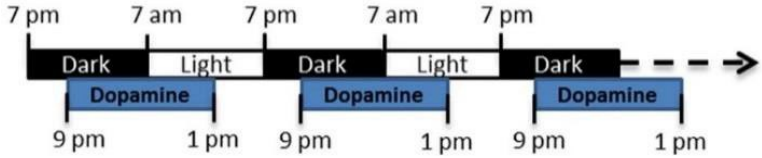
Figure 1A reproduced without modification from doi.: 10.3389/fneur.2019.01258.
Attribution 4.0 International (CC BY 4.0) https://creativecommons.org/licenses/by/4.0/

Continuous cerebroventricular administration of dopamine: A new treatment for severe dyskinesia in Parkinson's disease?

Neurobiology of Disease, Vol. 103, 2017, 24–31

http://dx.doi.org/10.1016/j.nbd.2017.03.013

Pump setting delivery in 6-OHDA rats:



Supplementary Image 1.

Dopamine delivery from the pump trough the rat brain cannula begin each day from zeitgeber time -10h (i.e. 9pm) to zeitgeber time 6 h (i.e. 1pm), over 16h during 30 days.
Image 1 & text reproduced without modification from C. Laloux et al. (CC BY-NC-ND 4.0)

https://creativecommons.org/licenses/by-nc-nd/4.0/

[Nose to Brain drug delivery]

Di Francesco, Valentina, et al. **Minimally invasive nasal infusion (MINI) approach for CNS delivery of protein therapeutics: A case study with ovalbumin.** [Open Access] Journal of controlled release: official journal of the Controlled Release Society: S0168-3659. doi: 10.1016/j.jconrel.2024.06.056

https://www.sciencedirect.com/science/article/pii/S0168365924004164?via%3Dihub

Investigate drug-evoked adaptations with different patterns of exposure.

Selected CNS Applications with iPRECIO Micro Infusion Pumps

Addiction/ Drug abuse liability

- Adversive effects of drug withdrawal in rats and mice
- Withdrawal Test
  - > Test potential compounds which may have similar effects in the same animals or reduce the signs of withdrawal
  - > Abrupt cessation

Perinatal opioid exposure leads to decreased social play in adolescent male and female rats: Potential role of oxytocin signaling in brain regions associated with social reward.

Hormones and Behavior 153 (2023): 105384

https://www.sciencedirect.com/science/article/abs/pii/S0018506X2300082X

Keywords: Neonatal opioid withdrawal syndrome, Morphine

Interruption of continuous opioid exposure exacerbates drug-evoked adaptations in the mesolimbic dopamine system

Neuropsychopharmacology (2020) | Published: 20 February 2020

https://doi.org/10.1038/s41386-020-0643-x

Subjects: Addiction, Reward

Discrimination Learning in Oxycodone-Treated Nonhuman Primates

Drug and Alcohol Dependence, Available online 27 November 2019, 107778

https://doi.org/10.1016/j.drugalcdep.2019.107778

Keywords: Opioid, Oxycodone, Naltrexone, Self-administration, Withdrawal, Cognition, Nonhuman primate

Convergent and Divergent Behavioral Changes Caused by Different Patterns of Morphine Exposure in Mice

International Narcotics Research Conference (INRC), Chicago, 9 - 14 of July 2017

CDKL5 PROTEIN SUBSTITUTION THERAPY RESCUES NEUROLOGICAL PHENOTYPES OF A MOUSE MODEL OF CDKL5 DISORDER

Human Molecular Genetics, ddy064, https://doi.org/10.1093/hmg/ddy064

https://academic.oup.com/hmg/advance-article-abstract/doi/10.1093/hmg/ddy064/4892297?redirectedFrom=fulltext

Differential effects of nicotine and nicotine withdrawal on fear conditioning in male rats [Open Access]

International Journal of Neuropsychopharmacology, pyaa024,

https://doi.org/10.1093/ijnp/pyaa024

Key words: Nicotine, PTSD, Fear Conditioning, Withdrawal

Additional Highlights: MiNDS

Fortunately for us, iPRECIO® too. Playing our small part for Science.

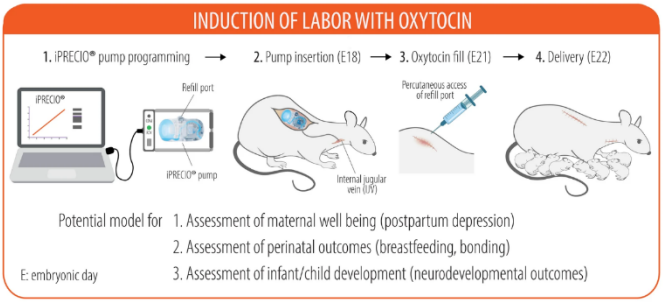
CC BY-NC-ND*,
Credit M. Scott Brauer
Miniaturized Neural System for Chronic, Local Intracerebral Drug Delivery (MiNDS)

https://www.media.mit.edu/projects/miniaturized-neural-system-for-chronic-local-intracerebral-drug-delivery/press-kit/

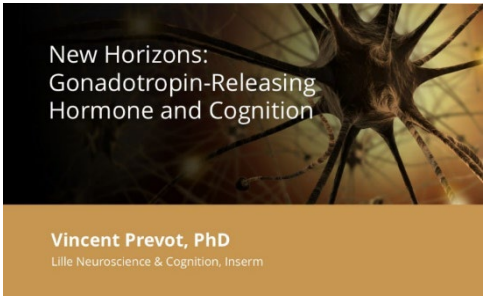
Miniaturized neural system for chronic, local intracerebral drug delivery
Science Translational Medicine 24 Jan 2018: Vol. 10, Issue 425, eaan2742
DOI: 10.1126/scitranslmed.aan2742
http://stm.sciencemag.org/content/10/425/eaan2742

Focal, remote-controlled, chronic chemical modulation of brain microstructures
PNAS July 10, 2018 115 (28) 7254-7259; https://doi.org/10.1073/pnas.1804372115

Giri, Tusar, et al. **"Labor induction with oxytocin in pregnant rats is not associated with oxidative stress in the fetal brain."** Scientific reports 12.1 (2022): 1-12.
https://www.nature.com/articles/s41598-022-07236-x [Open Access]



Experimental schematic for labor induction with oxytocin in term pregnant rats. (A) A cartoon depicting the programming and implantation of iPRECIO pump in a pregnant rat followed by birth of healthy pups. Reproduced without modification under Attribution 4.0 International (CC BY 4.0) https://creativecommons.org/licenses/by/4.0/



"We are proud to have played a part of **the dream experiment** to deliver exact rhythm of GnRH from wild type mice to Ts65Dn mice."

https://bit.ly/3s2YI3f

WED, SEPT 20, 2023 – 11:00 EDT / 17:00 CEST (Tech Methods Event)

https://insidescientific.com/webinar/new-horizons-gonadotropin-releasing-hormone-and-cognition/?utm_bmcr_source=PrimeTech

This webinar dives into the development and establishment of the gonadotropin-releasing hormone (GnRH) system and the importance of its first postnatal activation.

Key Topics Include:

- Realizing that the hypothalamus plays a vital role in the control of sensory and cognitive functions
- Learning about minipuberty and its key role in brain development

References:

Manfredi-Lozano, Maria, et al.
GnRH replacement rescues cognition in Down syndrome.
Science 377.6610 (2022): eabq4515.
https://www.science.org/doi/abs/10.1126/science.abq4515

Prévot, Vincent, Manuel Tena-Sempere, and Nelly Pitteloud.
New Horizons: Gonadotropin-releasing hormone and cognition.
The Journal of Clinical Endocrinology & Metabolism (2023): dgad319.
https://academic.oup.com/jcem/advance-article-abstract/doi/10.1210/clinem/dgad319/7187944

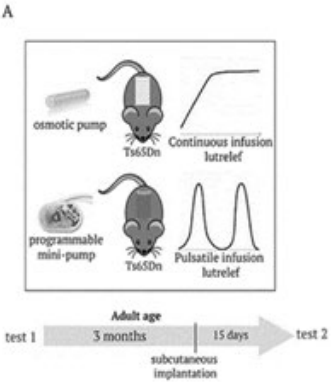
WO2020221821A1 Pulsative gnrh administration for treating cognitive disorders [Open Access]

Vincent PREVOT Andrea MESSINA Paolo GIACOBINI Valérie LEYSEN Maria MANFREDI LOZANO

https://patents.google.com/patent/WO2020221821A1/en?oq=WO2020221821A1

Excerpts from patent application WO2020221821A1 (Down syndrome DS - Ts65Dn mice, Route of administration (RoA) -SC)

"Without access to the iPRECIO micro infusion pumps, our experiments would have been almost impossible. As they require an injection every 3h over a period of 2 weeks, it would have been very difficult to impossible to have performed the experiment manually."



Reitz, Cristine J., et al. **A brief morning rest period benefits cardiac repair in pressure overload hypertrophy and postmyocardial infarction.**
JCI insight 7.22 (2022). [Open Access]
https://insight.jci.org/articles/view/164700

“We used the iPRECIO programmable infusion pump system in order to time drug administration specifically over the 4-hour period of additional rest and implantable radiotelemetry to follow hemodynamics, with both approaches eliminating the stress of animal handling.”

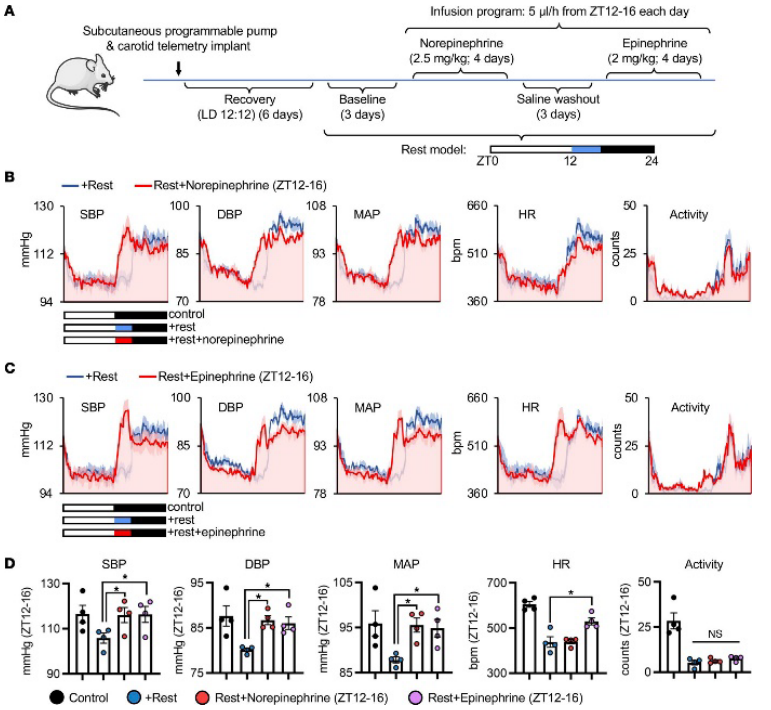
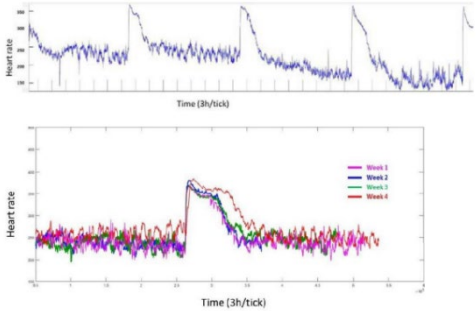


Figure 6. A brief period of morning rest delays the onset of sympathetic activity to benefit cardiovascular hemodynamics. (A) Schematic of experimental design. Healthy mice were implanted with both a subcutaneous programmable iPRECIO infusion pump and carotid artery radiotelemetry. For full details see
Reitz, Cristine J., et al. "**A brief morning rest period benefits cardiac repair in pressure overload hypertrophy and postmyocardial infarction.**"
JCI insight 7.22 (2022). [Open Access] https://insight.jci.org/articles/view/164700
Published in Volume 7, Issue 22 on November 22, 2022

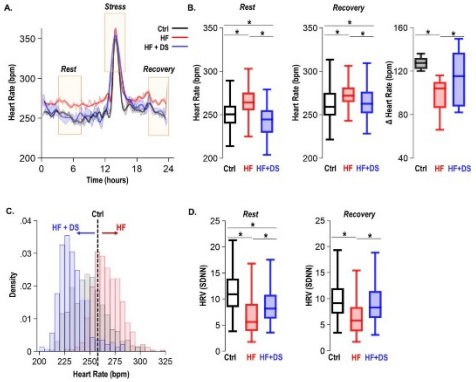
”Timed delivery of pharmacological agents. The pump was programmed for 1 hour delivery of Isoproterenol (mild transient β-AR stress for 1 hr) at 30ul/hr, total dose of 2mg/kg/day, once a day at the same time (1pm)”

Dey, Swati, et al. "**Mitochondrial ROS drive sudden cardiac death and chronic proteome remodeling in heart failure.**" [Open Access] *Circulation research* 123.3 (2018): 356-371.
https://www.ahajournals.org/doi/full/10.1161/CIRCRESAHA.118.312708



The animal model used in this research involved guinea pigs subjected to ascending aortic constriction (AC) and daily administration of isoproterenol via a programmable iPRECIO pump. This model simulates heart failure and sudden cardiac death, progressing from compensated hypertrophy to heart failure within weeks. The protocol ensures consistent β-adrenergic stimulation and avoids stress from manual injections, improving reproducibility and reducing confounding factors.

Joshi, P., Estes, S., DeMazumder, D., Knollmann, B. C., & Dey, S. (2023). “**Ryanodine receptor 2 inhibition reduces dispersion of cardiac repolarization, improves contractile function, and prevents sudden arrhythmic death in failing hearts.**” [Open Access] *Elife*, 12, RP88638. https://elifesciences.org/articles/88638

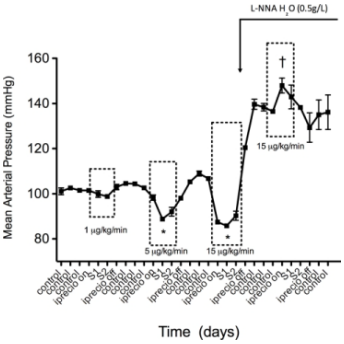


Dantrolene treatment decreases heart rate and improves chronotropic competency in heart failure (HF). (**A**) Plot shows heart rate derived from 24 hr continuous electrocardiogram (ECG) recordings. The animals were subjected to mild transient β-AR stress for 1 hr. Continuous ECG analysis was performed at the following time points: resting heart rate (pre-stress); transient stress and, post-stress recovery (4 hr post-stress)

All animal work followed IACUC-approved protocols at the respective institutions. A pressure overload model of HF and SCD was surgically generated with ascending aortic constriction (AC) and a daily bolus of low-dose isoproterenol (2 mg/kg/day) for β-adrenergic challenge. The surgical procedure and animal model have been previously described in detail (Dey et al., 2018).

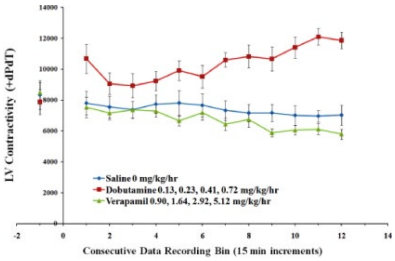
Additional Application Examples

5-HT **dose response** with control period : 5-25 greater sensitivity



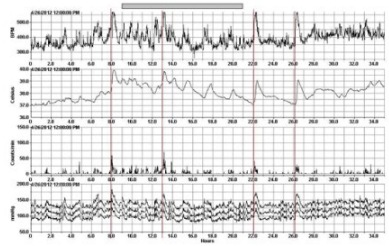
Drug Delivery: Enabling Technology for Drug Discovery and Development.
iPRECIO® Micro Infusion Pump: Programmable, Refillable, and Implantable
Tsung Tan, Stephanie W. Watts, and Robert Patrick Davis
Front Pharmacol. 2011; 2: 44. Published online 2011 July 29.
doi: 10.3389/fphar. 2011.00044
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149148/

Dose response: Dobutamine, verapamil & saline 3 test articles per animal (pump)



Drug Delivery: Enabling Technology for Drug Discovery and Development.
iPRECIO® Micro Infusion Pump: Programmable, Refillable, and Implantable
Tsung Tan, Stephanie W. Watts, and Robert Patrick Davis
Front Pharmacol. 2011; 2: 44. Published online 2011 July 29.
doi: 10.3389/fphar. 2011.00044
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149148/

100nl bicuculline methiodide (BMI) **bolus** injections



Zaretsky D.V., Zaretskaia M.V., Durant P.J., Rusyniak D.E.
The use of microinfusion pump to perform intrahypothalamic injections in conscious rats.
Neuroscience 2012, New Orleans, USA.,
October 13th - 17 2012

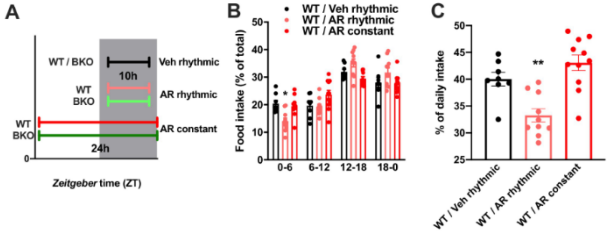
http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2964&sKey=87d8b951-316f-466a-9eb7-4b154d0bbd2c&cKey=b4b8338f-9bd2-44e2-bcf4-6e05a36cbbcb&mKey=%7b70007181-01C9-4DE9-A0A2-EEBFA14CD9F1%7d

Comparison of arterial pressure and plasma ANG II responses to three methods of subcutaneous ANG II administration
Comparison of arterial pressure and plasma AngII responses to three methods of subcutaneous AngII administration
Kuroki M.T. . , Gregory D. Fink , John W. Osborn
American Journal of Physiology - Heart and Circulatory PhysiologyJul 2014, DOI: 10.1152/ajpheart.00922.2013
https://journals.physiology.org/doi/full/10.1152/ajpheart.00922.2013

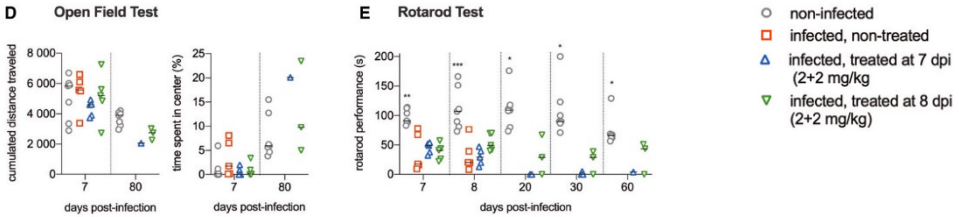
All things mouse with iPRECIO Programmable Pumps (IMS/SMP-300 and IMS/SMP-310R)

An adipokine feedback regulating diurnal food intake rhythms [Open Access]
Tsang et al.
RESEARCH ARTICLE Jul 9, eLife 2020;9:e55388 DOI: 10.7554/eLife.55388
https://elifesciences.org/articles/55388 *Excerpts and Figures 8 (A)-(C) reproduced Tsang et al. based on Attribution 4.0 International (CC BY 4.0),* https://creativecommons.org/licenses/by/4.0/ *No modifications made.* (Adipoq-deficient mice or wild-type mice - 8 weeks of age, Route of Administration (RoA -ICV))

Figure 8 A-C Rhythmic AdipoRon administration rescues food intake rhythms and body weight in obese male mice.
(A) Treatment regimen and groups. (B–D) Daily food intake profiles (B), relative light phase food intake (C) and total daily food intake



A combination of two human monoclonal antibodies cures symptomatic rabies [Open Access] EMBO Mol Med (2020)e12628, https://pubmed.ncbi.nlm.nih.gov/32945125/ *Excerpts and text reproduced from Dias de Melo et al. based on Attribution 4.0 International (CC BY 4.0),* https://creativecommons.org/licenses/by/4.0/ *No modifications made.* (Eight-week-old female SPF Balb/cJRj mice, RoA -ICV)



Mouse behavioral testing. The tested animals were non‐infected (n = 3 mice with iPRECIO pump + n = 4 age‐related mice without iPRECIO pump), infected non‐treated (n = 5), infected and treated at 7 dpi (n = 5, mice #9 to #13), and infected and treated at 8 dpi (n = 5, mice #24 to #28).

Sympathetic Overactivity in CKD Disrupts Buffering of Neurotransmission by Endothelium-Derived Hyperpolarizing Factor and Enhances Vasoconstriction. Cao et al. (CD-1 mice (6 weeks old) 20–24 g, RoA -ICV)
Journal of the American Society of Nephrology. JASN July 2020, ASN.2020030234; doi. :10.1681/ASN.2020030234
https://journals.lww.com/jasn/fulltext/2020/10000/sympathetic_overactivity_in_ckd_disrupts_buffering.13.aspx

Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through α7nAChR+ splenocytes [Open Access]. Inoue et al. J Clin Invest. Doi: 10.1172 / JCI83658, April 18, 2016
https://www.jci.org/articles/view/83658 (Male mice, 8–12 weeks of age, 20–25 g, RoA -IV)

More Translational Preclinical Models:

Programming of clinical dose regimens using iPRECIO pumps in the different animal models.

1) Major reason for the lack of an animal model for labor induction is the technical difficulty associated with delivering a gradually escalating dose of intravenous Oxytocin in a free moving animal [1]

2) More translational preclinical models: Protocol closely mirrors the clinical profile of infants exposed to opioids in utero [2]

3) To our knowledge, this was the first study to administer humanized doses of antifungal treatment to rats via implantable iPRECIO pumps; this permitted the use of a dosing schedule that closely mimicked intermittent dosing based on the PK profile of micafunguin in humans [3]

4) In our study, we employed a programmable subcutaneous pump to administer clinically relevant doses of cefepime in mouse plasma and the gastrointestinal tract. [4]

References:-

[1] Giri, Tusar, et al. "**Labor induction with oxytocin in pregnant rats is not associated with oxidative stress in the fetal brain.**" [Open Access] Scientific reports 12.1 (2022): 3143.
https://www.nature.com/articles/s41598-022-07236-x Keywords: Neonatal opioid withdrawal syndrome, Morphine

[2] Harder, Hannah J., et al. "**Perinatal opioid exposure leads to decreased social play in adolescent male and female rats: Potential role of oxytocin signaling in brain regions associated with social reward.**" Hormones and Behavior 153 (2023): 105384. https://www.sciencedirect.com/science/article/abs/pii/S0018506X2300082X
Keywords: Neonatal opioid withdrawal syndrome, Juvenile play, Social play, Morphine

[3] Warn, Peter, et al. "**Intermittent micafungin for prophylaxis in a rat model of chronic Candida albicans gut colonization.**" [Open Access] Journal of Antimicrobial Chemotherapy 75.10 (2020): 2919-2924
https://academic.oup.com/jac/article/75/10/2919/5877001
Topic: candida albicans, feces, rats, micafungin, microbial colonization, prevention

[4] Rodrigues, Marinelle, et al. "**Susceptible bacteria "can" survive antibiotic treatment in the mammalian gastrointestinal tract without evolving resistance.**" Cell Host & Microbe (2024).
https://www.cell.com/cell-host-microbe/abstract/S1931-3128(24)00016-7 Keywords: antibiotic resistance, antibiotic persistence, antibiotic tolerance, mammalian GI tract, bacterial survival, Escherichia coli, bacterial virulence

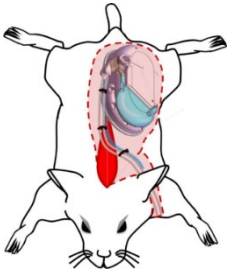
Hot off the press: Dose regimens.

"**To mimic the extended-release formulation**, iPRECIO programmable minipumps (SMP-200) delivered a constant infusion of 8.33ug/h. The pump was refilled every third day and replaced when the battery expired. Daily treatment with 0.2 mg/kg/d naltrexone lasted for 5 months for reinstatement studies and for 3 months for antinociception studies."

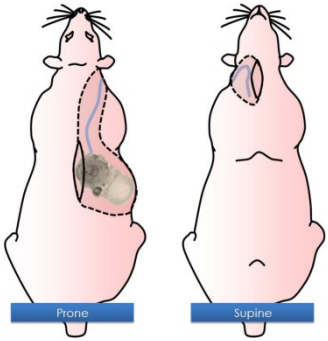
Withey, Sarah L., Jack Bergman, and Carol A. Paronis. "**The effects of chronic naltrexone on reinstatement of opioid-induced drug-seeking behavior and antinociception**." *Journal of Pharmacology and Experimental Therapeutics* 389.1 (2024): 5-14. https://jpet.aspetjournals.org/content/389/1/5.abstract

Example Pump implantation site and drug administration site

Intravenous Administration

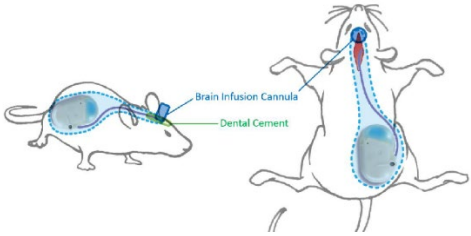


SMP-310R

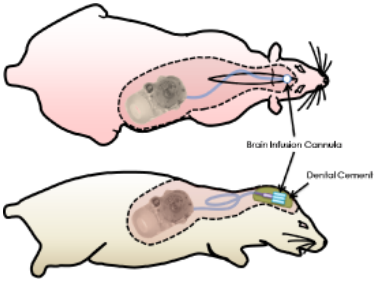


SMP-200

Intracerebral Administration



SMP-310R



SMP-200

Support Materials

Technical Note/Surgical Protocol :

-Recommendation for Intravenous Administration.
-Recommendations for Subcutaneous Administration.
-Recommendations for Intraperitoneal Administration.
-Recommendations for Intracerebral Administration.
-Recommendations for Intrathecal Administration.

References

An Improved Method of Implanting a Programmable Continuous Infusion Pump in Mice. (C57BL/6 mice (44 to 52 day old , 19 to 25 g), Route of administration (RoA) - SC
68th AALAS National Meeting, October 15 to 19th 2017, Austin Convention Center, 500 E. Cesar Chavez Street, Austin, TX 78701, U.S.

Surgical Videos

Mouse Surgeries (SMP-300 / SMP-310R)

SMP-300 / SMP-310R with SC administration and general preparation video

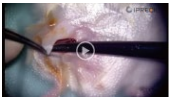
https://drive.google.com/drive/folders/0B0pySJ1uXUqSVFBSVVAzTlZHaWc?resourcekey=0-kOMVOKHst22jjOxNE-5RyA&usp=sharing

SMP-300 / SMP-310R with IP administration

https://drive.google.com/drive/folders/0B0pySJ1uXUqSd1BNdDVZeEFQUWM?resourcekey=0-a8bb3m0IFMGZYvBbfFEp-w&usp=sharing

SMP-300 / SMP-310R with IV Jugular administration

https://drive.google.com/drive/folders/0B0pySJ1uXUqSbENyQ21nY2REcHM?resourcekey=0-9HPwbMFKCRttX5G7lG7dUw&usp=sharing



SMP-300 / SMP-310R with IV femoral administration

https://drive.google.com/drive/folders/0B0pySJ1uXUqSdlFtVFdJMFFncWM?resourcekey=0-GMNTGvE5ZXG9j0qS_QPNAw&usp=sharing

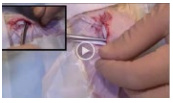
SMP-300 / SMP-310R with ICV administration

https://drive.google.com/drive/folders/0B0pySJ1uXUqSUGxHWkdLTXMwSEk?resourcekey=0-Uirh6Hx2Z0VlVpskbca7Tw&usp=sharing

Refilling Video and Refiling FAQ

https://drive.google.com/drive/folders/0B0pySJ1uXUqSX203d1l4bGsxOG8?resourcekey=0-OU5m2j7nCRxfhfJ4u3uSeA&usp=sharing

Rat Surgeries (SMP-200)



Surgery Training Videos

https://drive.google.com/drive/folders/0B0pySJ1uXUqSR2kzLVlMbWtRNUE?resourcekey=0-2iWx-iiDd7sJJPI2AZIV4A&usp=sharing

We have been working on surgical videos which we hope will help our users.
These are for the SMP-200 pumps you have been using
> We have been working surgical videos unfortunately, they are not complete yet.
> Feedback on the videos were provided by other surgeons (word document attached)
> We have been working with Vetbiotech, www.vetbiotech.com to complete them.

References

STAR (Structured Transparent Accessible Reproducible) Protocols Publication (Cell Press)
Giri, Tusar, and Arvind Palanisamy. "**Protocol for continuous intravenous drug delivery with implantable iPrecio pump in free-moving rats and mice.**" [Open Access]
STAR protocols 5.3 (2024): 103224. https://www.sciencedirect.com/science/article/pii/S2666166724003897
Subject areas: Health Sciences, Model Organisms, Neuroscience

iPRECIO® Key Features

> Accurate patented Rotary Finger Method
- Every pump is factory tested and calibrated
- Better than ±5% accuracy
- Programmable infusions protocols (simple and complex)

> Totally implanted in subcutaneous space

> Refillable (reservoir) percutaneously via refill port with re-sealable septum

> With iPRECIO® catheters, test your drug's effects nearly anywhere

> Easy to use software for infusion protocol programming

Implantable

The pump can be completely implanted in small laboratory animals subcutaneously. Thus, the animal moves freely without any restrain (i.e. tethering) during drug infusion. Additionally, infection risk is reduced, and the animal is likely to be significantly less stressed than in a tethered infusion model.

Refillable

You can replenish or exchange saline and/or any medical fluid in the pump via percutaneous access to the pump refill septum and reservoir after implantation of the pump. Recovery from surgery or washouts may be planned with saline in the reservoir. Long-term drug infusion can be maximized to battery life of the pump.

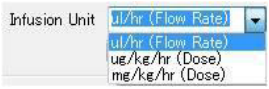
Precision

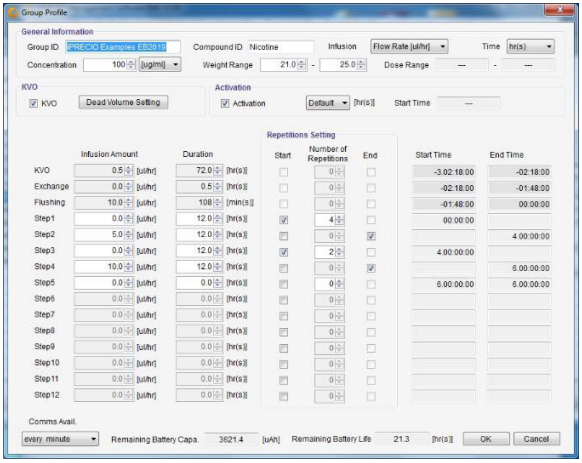
The technology driving the infusion is a patented "Rotary Finger" method. This method is a unique form of peristalsis. The precise "micro-stick" pushes a rubber tube in the pump in a uniform and sequential manner. The accuracy of iPRECIO is +/-5%.

Programmable

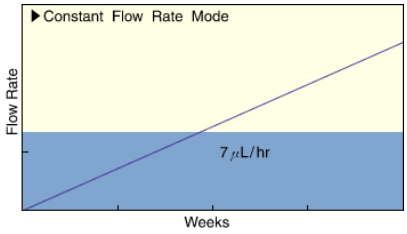
> SMP-310R 15 steps for flow rate or dose programming : 0.0-10.0 ul/hr with repeat mode

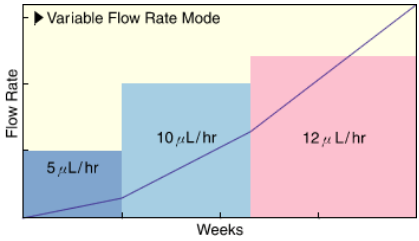
Each flow profile may contain up to 15 doses or flow rate steps. A single step would mean a fixed continuous dose or flow-rate for the study duration. A more complex infusion profile will contain more than 1 step and may contain up to 15 steps. KVO and dead volume flushing functions may be programmed within the 15 programmable steps.

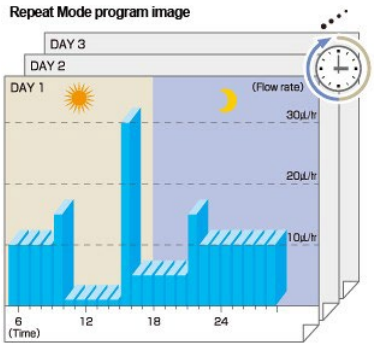


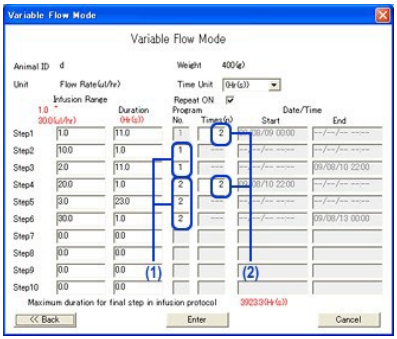


> SMP-200 10 steps for flow rate programming : 0, 0.2, 0.5 & 1.0 - 30.0 ul/hr with repeat mode







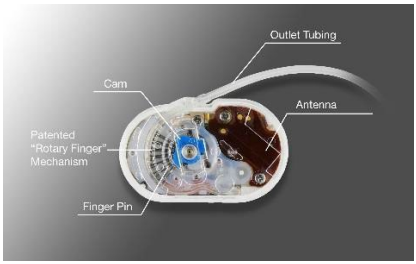


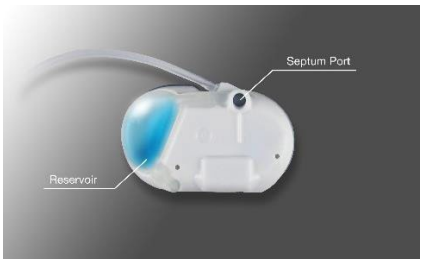
iPRECIO® is an Ultimate Choice

This implantable infusion pump uses a patented, microprocessor controlled peristalsis mechanism for accurate controlled flow. It is the only implantable and programmable pump for small laboratory animals. iPRECIO® can infuse fluids continuously for as long as six months and it can be refilled via a percutaneously accessible port.

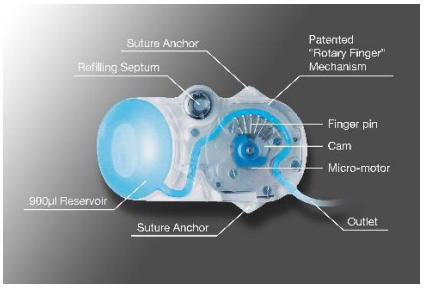
iPRECIO® Pump's Structure

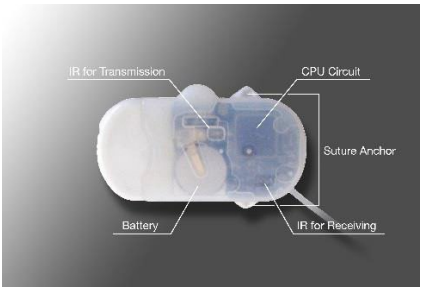
> SMP-310R





> SMP-200





iPRECIO® Management System

> SMP-310R

iPRECIO® Management System is sold as IMS-310R which consists of data communication device (UCD-X10R) and Management Software, User Manual.

Curious to learn more?
Download Application to try it out here.
https://www.iprecio.com/support/tabid/262/Default.aspx

> SMP-200

iPRECIO® Management System consists of:
- Data Communication Device
- USB cable, 2 AAA batteries
- iPRECIO® Management Software Installation CD
- iPRECIO® User Manual

Curious to learn more?
Download Application to try it out here.
https://www.iprecio.com/support/tabid/262/Default.aspx

iPRECIO® Battery Life

> SMP-310R

Com.	Per minute		Every 2 hours		Every 6 hours		Every 24 hours		None	
Flow rate	Driving hours	Driving days	Driving hours	Driving days	Driving hours	Driving days	Driving hours	Driving days	Driving hours	Driving days
0.1	157	6.5	528	22.0	1063	44.3	1542	64.3	1628	67.8
0.5	155	6.5	476	19.8	887	37.0	1214	50.6	1266	52.8
1.0	153	6.4	428	17.8	742	30.9	959	40.0	991	41.3
5.0	137	5.7	263	11.0	344	14.3	357	14.9	362	15.1
8.0	127	5.3	207	8.6	243	10.1	243	10.1	245	10.2
10.0	121	5.0	178	7.4	196	8.2	200	8.3	201	8.4

Flow Rate Unit : µL/hr
* Table above outlines the maximum battery life for the programmed protocol and pump switch on time.
Exact battery life will be dependent on pump switch on time, programmed infusion protocol, and selected communication availability(Com.). iPRECIO Management software helps the user calculate battery life for selected programming.

> SMP-200

Flow Rate	Infusion Time		Total Volume
	Time (h)	Days (approx.)	
30.0 µL/hr	196 hr	1 week	5.8 ml
19.0 µL/hr	307 hr	1.8 weeks	5.8 ml
8.5 µL/hr	669 hr	1 month	5.6 ml
1.0 µL/hr	4,328 hr	6 months	4.3 ml

Model	SMP-310R / IMS-310R	SMP-200 / IMS-200
Appearance of the pump	 24.8(L) x 15.0(W) x 7.2 (H) mm, Max. height 7.5mm	 38.7 (L) X 19.2 (W) X 9.7 (H) mm
Type	Implantable SC	Implantable SC
Volume / Weight	2.26cc / 3.4g	7.20cc / 7.9g
Animal Species	Mouse or larger	Rats or larger
Reservoir Volume	130 µL	900 µL
Flow Rate (Setting Resolution)	0.0 – 10.0 µL/hr (0.1µL/hr)	0.0, 0.2, 0.5&1.0 – 30.0µL/hr (0.1µL/hr)
Flow Steps / Repeat	15 / Yes	10 / Yes
Battery Life	0 & 0.1 ul/hour 67 days 1 µl/hour up to 41 days 10 µl/hour up to 8 days	0, 0.2, 0.5, 1 µl/hour - 6 mths 2.5 µl/hour - 86 days 30 µl/hour - 8 days
Programmable	Wireless Preprogrammable	Preprogrammed prior to implantation
Wireless Distance	1 – 6m	-
Communication Availability	1m, 1h, 2h, 4h, 6h, 12h, 24h and NONE (8 choices)	-
PC OS compatible	Windows 10 & 11	

Compatible solvents for SMP-300, 310R and SMP-200

* Tested for both SMP-200 & SMP-300 / SMP-310R
* Tested in SMP-200 Pump Only

(same materials and manufacturing process) and expected to be compatible when compatible. Also, not compatible when not compatible.

Compatible Solvents

Acids, with pH 2 or weaker *
Bases, with pH less than 13 *
Buffered Phosphate Saline (PBS) *
Culture Media (1% benzyl alcohol) *
Cyclodextrin *
Dextrose, up to 5% in water or saline *
N,N-Dimethyl formamide (DMF), up to 25% in water *
DMSO 50% and water or saline 50% *
DMSO, up to 50% in ethanol (≤15%) and water *
DMSO 5% and PEG400 95% *
50% DMSO + 50% Propylene Glycol *
DMSO 50% and water 50% *
DMSO 50% + 15% ethanol and 35% water *
Dulbecco's Modified Eagle Medium (D-MEM) (1X), liquid *
Ethanol, up to 50% in water *
Glycerin, up to 75% in water *
Glycerol 100% *
1-Methyl-2-Pyrrolidone, up to 12.5% in water *
Propylene Glycol *
Ringer's solution (without lactate) *
Saline, 0.9% (or other aqueous salt solution) *
Triacetin, up to 5% in water *
Tween 80, up to 2% in water *
Water, distilled *
PEG200 100% *
Solutol® 15% in water *

Viscosity up to 20 cp is ok.
(Higher viscosity not tested due to the use of 27G needles.
Difficulty to aspirate solution with 27G needle)

Short term use only (1 - 2month)

PEG300 100% * (< 45 days)
PEG400 100% *
Cremophor EL 25% in water * (< 30 days)
PEG400/Propylene Glycol/Water 30 : 50 : 20 * (< 30 days)

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