

Micro infusion pump



Implantable, Programmable and Refillable

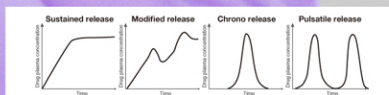
Application Examples from peer reviewed publications

**NEW
310R**

+40% battery life
for 0.1ul/hr (No comms)

+25% battery life
for 0.5ul/hr (No comms)

+20% battery life
for 1ul/hr (No comms)



All things mouse Pg.27-28

Cardiovascular Pg.13, 16, 18 & 25

GLP & Toxicology Pg.15

Infectious Disease Pg.25

Metabolism Pg.5-8 & 28

Neuroscience Pg.9-11, 14, 19-24

Oncology Pg.14, 17-19, 26 & 27

Micro infusion pump

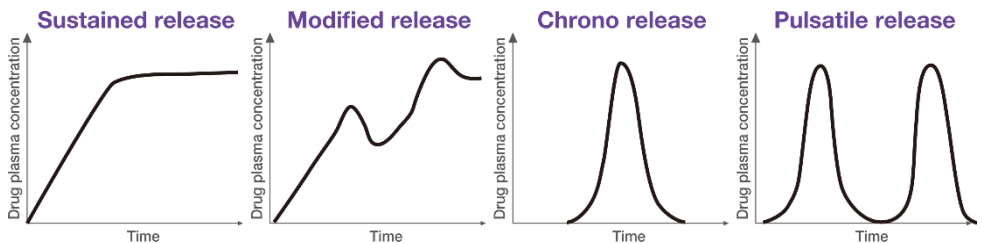


Implantable, Programmable and Refillable

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 :

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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 - d Ecto-domain phosphorylation promotes functional recovery from spinal cord injury, Scientific Reports
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 - Miniaturized Neural System for Chronic, Local Intracerebral Drug Delivery (MiNDS)
 - Labor induction with oxytocin in pregnant rats is not associated with oxidative stress in the fetal brain.
 - <US Patent App.> 20180161282 Methods & compositions for the treatment of seizure-related disorders.
 - < WO2020221821A1> Pulsative gnRH administration for treating cognitive disorders
 - Intermittent micafungin for prophylaxis in a rat model of chronic Candida albicans gut colonization
 - MitoTEMPO normalized ROS and prevented heart failure and arrhythmias
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Program what you need for overcoming:-

 - a. Narrow therapeutic index
 - i. Maximizing efficacy with timed infusion
 - ii. Minimizing toxicity with timed infusions
 - iii. Flexibility to program 101 discreet infusion flow-rates. (SMP-310R, 0.0 to 10.0µl/hours)
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Timed release of Test Article (TA), β OHB

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

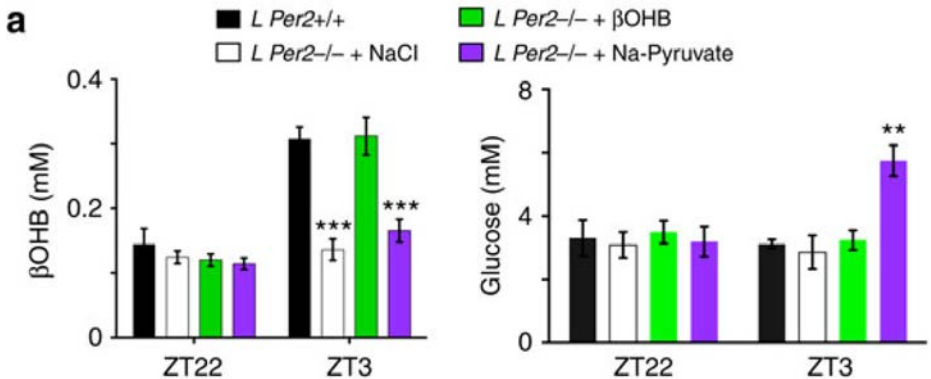


Figure 1 (Figure 4a in Full Article) **Rescue of food anticipation in *L Per2*^{-/-} mice by β -hydroxybutyrate.** (a) Timed release of β OHB (green) but not NaCl (white) or Na-Pyruvate (purple) in *L Per2*^{-/-} mice mimics the β OHB levels in plasma of *L Per2*^{+/+} control animals (black). Measured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

Figure 1 is reproduced from Liver-derived ketone bodies are necessary for food anticipation.

http://www.nature.com/ncomms/2016/160203/ncomms10580/full/ncomms10580.html?WT.ec_id=NCOMMS-20160205

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<http://creativecommons.org/licenses/by/4.0/>.

No changes were made for reproduction from Figure 4a of Chavan et al.

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 β OHB as FA signal, iPRECIO SMP-300 programmable minipumps were used to release β OHB 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 preceding feeding time.

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

Short methods or use of the pumps:

iPRECIO SMP-300 pumps were programmed to infuse saline vehicle at 2 μ l/h, or D- β OHB at 2 μ l/h, or Sodium pyruvate at 5 μ l/h, or coconut oil at 5 μ l/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 β OHB partially rescues FA.

Research Need:

Timed Release of β OHB 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 Emitter) 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>

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

<http://www.jlr.org/content/early/2015/07/13/jlr.M058149.abstract>

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>

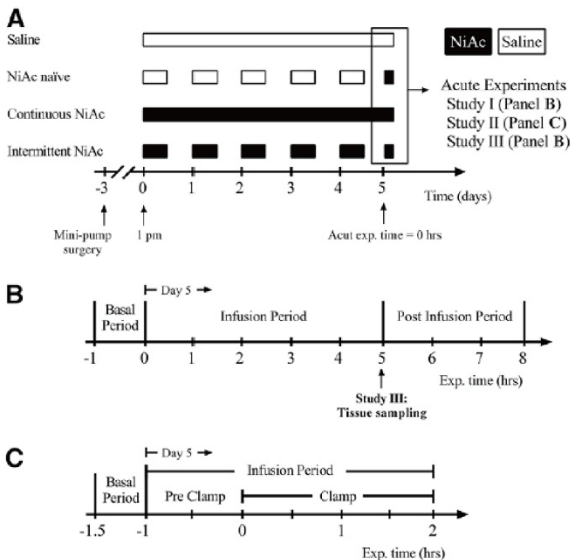


Fig. 2 (Figure 1 in Kroon et al.)

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-isoglycemic clamps).

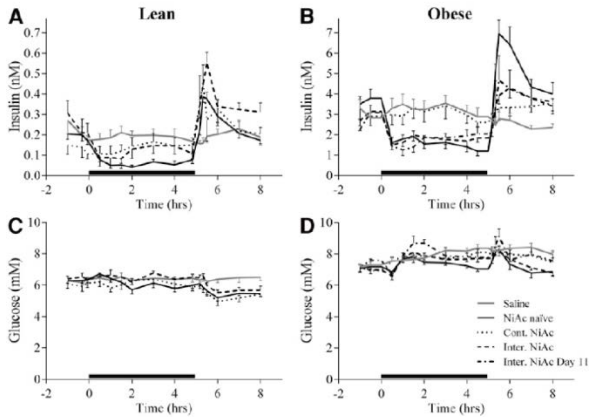


Fig. 3. (Figure 5 in Kroon et al.) Plasma insulin (A, B) and glucose (C, D) concentration in lean (left) and obese (right) following infusion of saline (lean $n = 5$, obese $n = 12$) or NiAc ($0.17 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) given acutely (NiAc naïve, $n = 7/\text{group}$) 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 \pm SE.

Figures 2 and 3 licensed material. © <2015> The American Society for Biochemistry and Molecular Biology. ·
 Warranties: None Publisher makes no representations or warranties with respect to the licensed material and adopt on its own behalf the limitations and disclaimers established by CCC on its behalf in its Billing and Payment terms and conditions for this licensing transaction.

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.

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>

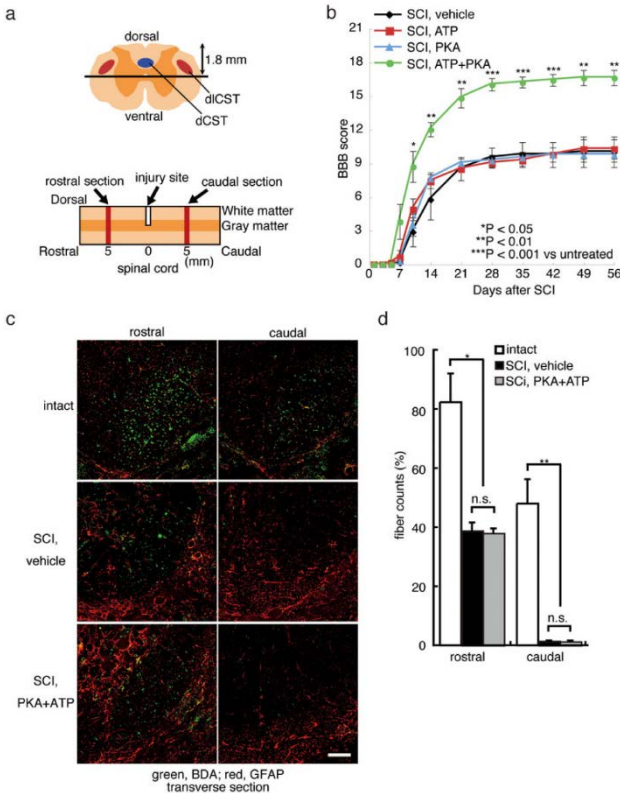


Figure 4 (Figure 1 from Suehiro et al)

| 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 PKA+ATP-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,

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.

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>

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

http://cdn2.hubspot.net/hubfs/212573/docs/Envigo/Envigo_Pharma_Dils_14.4.4.pdf?t=1460116975327

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 $30 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ 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;

<http://ajpheart.physiology.org/content/early/2012/12/10/ajpheart.00674.2012.abstract?sid=1c8187a4-b1a5-41e2-9e88-20610af15128>

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 $30 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$. 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 ¹²⁵I-UdR or ¹²⁷I-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 Delivery

Theranostics 2016, Vol. 6, Issue 12 2016; 6(12): 2278-2291. doi: 10.7150/thno.15898

<http://www.thno.org/v06p2278.htm>

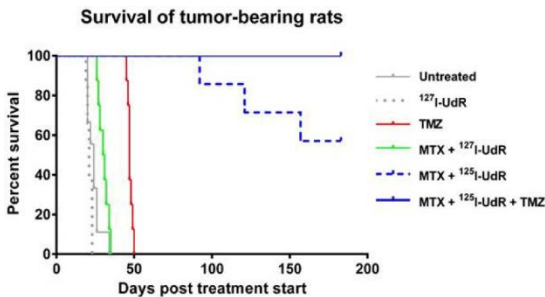


Figure 6. Kaplan-Meier plot showing that the survival benefit of neoadjuvant MTX + ¹²⁵I-UdR as stand-alone Auger-therapy (group4) or with concomitant, systemic TMZ chemotherapy (group5) was highly significant compared with the non-radioactive, but chemically identical treatment MTX + ¹²⁷I-UdR (group3, 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 ¹²⁵I-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 ¹²⁵I-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 ¹²⁵I-UdR or ¹²⁷I-UdR.

Results/significance

The multidrug approach including CED of MTX and the AEE-compound ¹²⁵I-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.

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.

Validation and use of the iPRECIO® micro-infusion pump on GLP studies
 J. Perron, V. Frenette, C. Copeman
 Charles River Laboratories Preclinical Services Montreal Inc., 20022 Transcanadienne, Steepleville, Quebec, Canada H4K 3P3

Introduction
 Low infusion rates are generally required for conduct of preclinical studies using non-treated routes of administration such as intraperitoneal, intracerebral or subcutaneous infusion or possible other single route delivery. Meeting these low flow demands with current infusion pumps can present various challenges. Various types of micro-infusion pumps can be used that ensure accurate dosing with providing reproducibility and accurate delivery which is important for the conduct of regulatory compliant studies. Our laboratory selected an implantable programmable micro-infusion pump, the iPRECIO® micro infusion pump, and evaluated its accuracy of delivery rate in compliance with regulatory compliant studies requiring very low infusion rates.

Material and Methods
Micro infusion pump
 The iPRECIO® micro infusion pump is indicated to allow infusion at rates of 1 to 10 µL/hr up to a concentration of 100 mg/mL. The accuracy of infusion is determined by programming, identifying the site of infusion, and the volume of infusion solution post-operatively, and the programming of dosing cycles occur over extended periods between hardware-based combination solutions.

Implantation
 The iPRECIO® micro infusion pump is supplied with an outer elastic sheath which may be cut and placed with the pump in a subcutaneous site on the back of the animal. The pump is connected to the animal with non-absorbable suture material. The infusion pump reservoir is located via a port which is easily located under the skin for palpation. The soft, bioabsorbable sheath is removed, leaving an incision site to the animal.

Pump delivery accuracy
 The iPRECIO® software functionality and the accuracy of the delivery of the micro infusion pumps were validated in order to allow its use in regulatory compliant studies. These infusion pumps were first used with a 0.1 Molar solution and programmed to deliver 10 µL/hr for 30, 60, 90, 120, 150, 180, 210, 240 and 480 hours with several parallel infusions of the infusion rate of the course of the given period. All infusions in the testing sequence lasted.

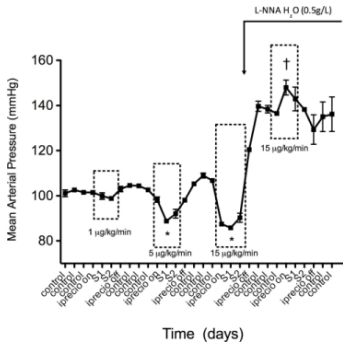
Results and Conclusion
 Our validation study demonstrated the successful implementation of the iPRECIO® pump with time complexity, accuracy, the ability to use the pump in a number of dosing schemes, and that the software accurately programmed the infusion pumps to deliver 1 to 10 µL/hr for 48 hours with an accuracy of > 10% of the intended dosage.

Percent recoveries were calculated and are presented below:

Flow Rate (µL/hr)	Target Volume (µL)	Actual Volume (µL)	% Recovery	SD
1	10	10.0	100.0	0.0
1	20	20.0	100.0	0.0
1	30	30.0	100.0	0.0
1	40	40.0	100.0	0.0
1	50	50.0	100.0	0.0
1	60	60.0	100.0	0.0
1	70	70.0	100.0	0.0
1	80	80.0	100.0	0.0
1	90	90.0	100.0	0.0
1	100	100.0	100.0	0.0
1	120	120.0	100.0	0.0
1	150	150.0	100.0	0.0
1	180	180.0	100.0	0.0
1	210	210.0	100.0	0.0
1	240	240.0	100.0	0.0
1	270	270.0	100.0	0.0
1	300	300.0	100.0	0.0
1	360	360.0	100.0	0.0
1	420	420.0	100.0	0.0
1	480	480.0	100.0	0.0
1	540	540.0	100.0	0.0
1	600	600.0	100.0	0.0
1	660	660.0	100.0	0.0
1	720	720.0	100.0	0.0
1	780	780.0	100.0	0.0
1	840	840.0	100.0	0.0
1	900	900.0	100.0	0.0
1	960	960.0	100.0	0.0
1	1020	1020.0	100.0	0.0
1	1080	1080.0	100.0	0.0
1	1140	1140.0	100.0	0.0
1	1200	1200.0	100.0	0.0
1	1260	1260.0	100.0	0.0
1	1320	1320.0	100.0	0.0
1	1380	1380.0	100.0	0.0
1	1440	1440.0	100.0	0.0
1	1500	1500.0	100.0	0.0
1	1560	1560.0	100.0	0.0
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1	1680	1680.0	100.0	0.0
1	1740	1740.0	100.0	0.0
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1	1860	1860.0	100.0	0.0
1	1920	1920.0	100.0	0.0
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1	2340	2340.0	100.0	0.0
1	2400	2400.0	100.0	0.0
1	2460	2460.0	100.0	0.0
1	2520	2520.0	100.0	0.0
1	2580	2580.0	100.0	0.0
1	2640	2640.0	100.0	0.0
1	2700	2700.0	100.0	0.0
1	2760	2760.0	100.0	0.0
1	2820	2820.0	100.0	0.0
1	2880	2880.0	100.0	0.0
1	2940	2940.0	100.0	0.0
1	3000	3000.0	100.0	0.0
1	3060	3060.0	100.0	0.0
1	3120	3120.0	100.0	0.0
1	3180	3180.0	100.0	0.0
1	3240	3240.0	100.0	0.0
1	3300	3300.0	100.0	0.0
1	3360	3360.0	100.0	0.0
1	3420	3420.0	100.0	0.0
1	3480	3480.0	100.0	0.0
1	3540	3540.0	100.0	0.0
1	3600	3600.0	100.0	0.0
1	3660	3660.0	100.0	0.0
1	3720	3720.0	100.0	0.0
1	3780	3780.0	100.0	0.0
1	3840	3840.0	100.0	0.0
1	3900	3900.0	100.0	0.0
1	3960	3960.0	100.0	0.0
1	4020	4020.0	100.0	0.0
1	4080	4080.0	100.0	0.0
1	4140	4140.0	100.0	0.0
1	4200	4200.0	100.0	0.0
1	4260	4260.0	100.0	0.0
1	4320	4320.0	100.0	0.0
1	4380	4380.0	100.0	0.0
1	4440	4440.0	100.0	0.0
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1	4560	4560.0	100.0	0.0
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1	4680	4680.0	100.0	0.0
1	4740	4740.0	100.0	0.0
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1	4860	4860.0	100.0	0.0
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1	4980	4980.0	100.0	0.0
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1	5160	5160.0	100.0	0.0
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1	5400	5400.0	100.0	0.0
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1	5520	5520.0	100.0	0.0
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1	5700	5700.0	100.0	0.0
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1	7020	7020.0	100.0	0.0
1	7080	7080.0	100.0	0.0
1	7140	7140.0	100.0	0.0
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1	8940	8940.0	100.0	0.0
1	9000	9000.0	100.0	0.0
1	9060	9060.0	100.0	0.0
1	9120	9120.0	100.0	0.0
1	9180	9180.0	100.0	0.0
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1	11820	11820.0	100.0	0.0
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1	12120	12120.0	100.0	0.0
1	12180	12180.0	100.0	0.0
1	12240	12240.0	100.0	0.0
1	12300	12300.0	100.0	0.0
1	12360	12360.0	100.0	0.0
1	12420	12420.0	100.0	0.0
1	12480			

Application Examples

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



Drug Delivery: Enabling Technology for Drug Discovery and Development.

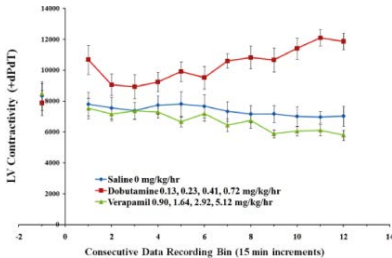
iPRECIO® Micro Infusion Pump:

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.

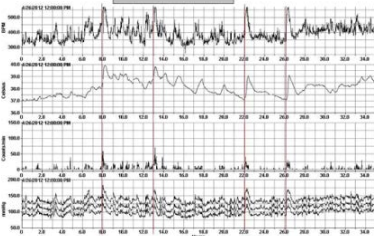
iPRECIO® Micro Infusion Pump:

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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.abstractionline.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 Physiology Jul 2014, DOI: 10.1152/ajpheart.00922.2013

<http://ajpheart.physiology.org/content/early/2014/06/30/ajpheart.00922.2013>

Webinar

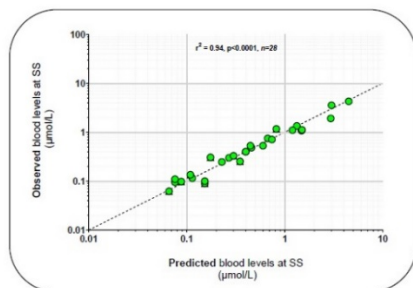
Webinar: Compound Delivery, PK-PD & Validation Studies in Oncology Studies

Christian Schnell, Associate Director Oncology NIBR Novartis in Basel

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

Programmable pumps for compounds delivery in oncology research: implication for refinement and reduction of animal use

Validation study in freely moving grouped housed nude mice and rats via an programmable iPRECIO pump using all tested doses and compound (i.v. via jugular vein)



- 2 species (mice and rats)
- 2 pumps (SMP-200 and SMP-310R)
- 3 tool compounds
- 24 doses
- 7 infusion rates (2.2 to 20 µl/h)

↳ $r^2 = 0.94, p < 0.0001, n = 28$

25 iPRECIO webinar, June 16th 2021 | Business Use Only

 **NOVARTIS** | Reimagining Medicine

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 KRAS^{G12C}." *Cancer Discovery* 12.6 (2022): 1500-1517.

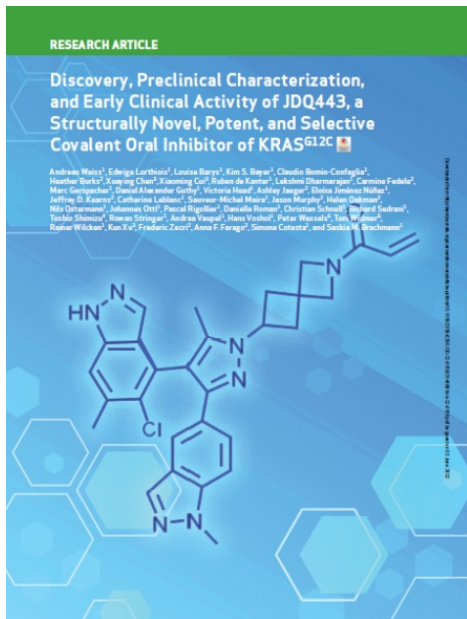
- iPRECIO SMP-310R Programmable pumps were used to better understand the relationship between PK, target occupancy, and efficacy.
- Continuous infusion demonstrated that Daily AUC rather than C_{max} or Time-over-threshold as the driver of efficacy of TDQ443.

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 μ L/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.”

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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>

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

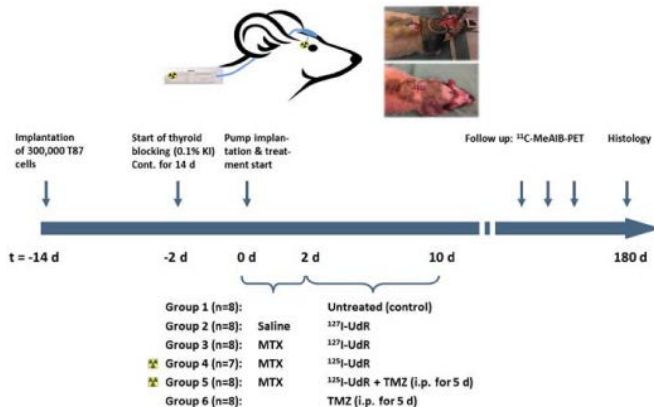


Figure 1 reproduced from Thisgaard et al. (CC BY-NC-ND 4.0)

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

<http://www.thno.org/v06p2278.pdf> Attribution-Non Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0)

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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

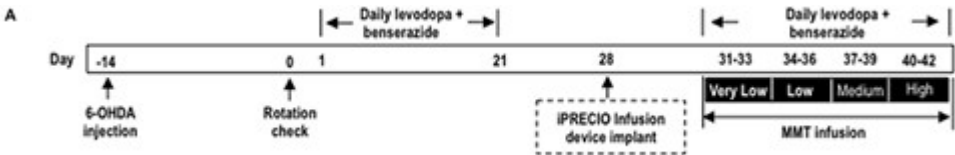


Figure 1A reproduced without modification from doi.: 10.3389/fneur.2019.01258.

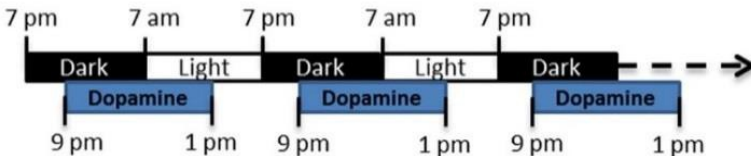
Attribution 4.0 International (CC BY 4.0) <https://creativecommons.org/licenses/by/4.0/>

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 through the rat brain cannula begins each day from zeitgeber time -10h (i.e. 9pm) to zeitgeber time 6h (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)

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Rhythmic Release of Corticosterone Induces Circadian Clock Gene Expression in the Cerebellum

Neuroendocrinology. 2019 Sep 27. doi: 10.1159/000503720

<https://www.karger.com/Article/Abstract/503720>

Key words: Cerebellum, Circadian, Clock gene, Corticosterone, Suprachiasmatic nucleus, iPRECIO programmable micropump

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

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

<https://www.fourwav.es/view/324/abstracts/#5203>

Mechanisms specific to methamphetamine-associated memory disruption by nonmuscle myosin II inhibition

420.01 / SS23, Neuroscience Annual Meeting 2017, Nov 11th to 15th 2017 Washington DC

<http://www.abstractsonline.com/pp8/#!/4376/presentation/16699>

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)

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

<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

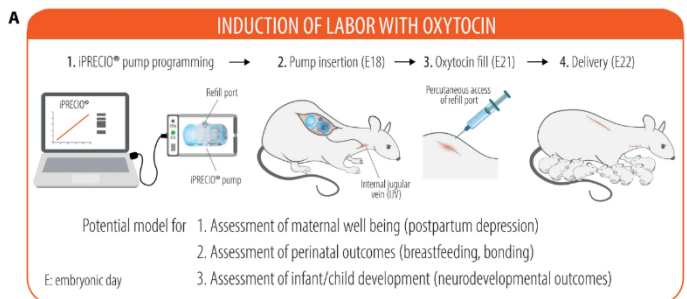
PNAS July 10, 2018 115 (28) 7254-7259; <https://doi.org/10.1073/pnas.1804372115>

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

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Additional Highlights: United States Patent Application 20180161282

Methods and compositions for the treatment of seizure-related disorders by Adamas Biopharmaceutical Inc. (<https://www.adamaspharma.com/>) includes references to iPRECIO Micro Infusion Pump use in Examples 13 to 16. In example 13, “The PK parameters (C_{max}, T_{max}, T_{1/2}, AUC) of 200 mg IR lacosamide BID and 400 mg ER lacosamide QD in humans can be replicated in rats using programmable

- CNS side effects were compared when delivered as a continuous infusion in rats to simulate an extended release (ER) plasma profile or as a bolus to simulate an immediate release (IR) plasma profile.
- CNS side effects were measured as an impairment of motor coordination in rodents using the rotor-rod.

Excerpts from US Patent Publication 20180161282

Example 13: Pharmacokinetic Study of Lacosamide Administered by Continuous Subcutaneous Infusion to Rats for 7 Days

The objective of this study is to demonstrate that the PK profile from a standard regimen of 200 mg IR lacosamide BID in humans, along with a novel PK profile of 400 mg ER lacosamide QD, can be replicated in rats using programmable subcutaneous infusion pumps. Jugular vein cannulated male and female Sprague Dawley rats weighing between 240-260 grams are used for this study. Rats are implanted with programmable infusion pumps (iPRECIO SMP-200)

Example 14: - related to training for Rotor-rod Training and Test

Following the period of acclimation, rats are surgically implanted with subcutaneous programmable pumps (iPRECIO), per the manufacturer's instructions. Prior to implantation, pumps are pre-programmed and filled with sterile 0.9% saline according to the manufacturer's instructions. Implantation is done under anesthesia by using aseptic techniques.

Three days following pump implantation surgery, rats are pre-trained on the rotarod and assigned to treatment groups based on their body weights.

Infusion of lacosamide commences on day four post-pump implantation surgery. Baseline measurements are made on the rotarod on Day 4. Immediately thereafter, saline in the iPRECIO pumps is withdrawn and the pump is refilled with lacosamide solution (25 mg/mL in 0.9% saline). Pumps are refilled during the 7 day period as necessary, through the access port of the iPRECIO pump.

Excerpts from US Patent Publication 20180161282 continued.

for Simulated BID dosing

TABLE EX 13A : Study Design and Infusion Protocol

Group	Number of animals	Dose Period ²	Dose rate/rat ¹ (mg/h/rat)	Concentration in pump (mg/mL)	Pump Flow rate (µL/h)	Plasma Collection Times (hours)
1	4	0 - 2 h	0.59	20	29.5	1, 4, 8, 14, 20
		2 - 12 h	0.12	20	6	84, 144, 158
2	4	0 - 2 h	0.59	20	29.5	2, 6, 12, 18
		2 - 12 h	0.12	20	6	24, 98, 156, 168

¹ Lacosamide dose estimates are based on average animal body weight of 250 g

² Pump infusion protocol is repeated every 12 hours for a total of 7 days

For further information see patent application,

<https://patents.google.com/patent/US20180161282A1/en?q=20180161282>

WO2020221821A1 Pulsative gnRH administration for treating cognitive disorders

[Open Access]

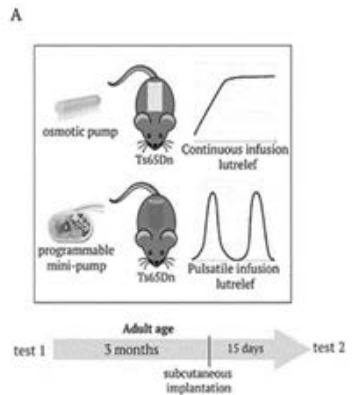
Vincent PREVOT Andrea MESSINA Paolo GIACOBINI
Valérie LEYSEN Maria MANFREDI LOZANO

<https://patents.google.com/patent/WO2020221821A1/en?q=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."

"Adult mice were implanted with osmotic minipumps (1002, Alzet, USA) receiving continuous infusion of vehicle (sterile 0.1M PBS) or LUTRELEF® (0.25 pgr/ 3h) (Ferring Pharmaceuticals, Switzerland); or with a programmable micro infusion pump (SMP-300, iPRECIO, Japan) receiving pulsatile infusion of vehicle or LUTRELEF® (every 3 hours, a peak of 0.25 pg during 10 min), mimicking GnRH/LH pulsatility reported in WT mice (Czieselsky et al, 2016), and a basal infusion with a low dose (0.0025 pg/10 min) for the rest of the time. The pumps were placed under the skin on the back of the mouse. Both olfactory and cognitive deficiencies were confirmed before in these animals. One week after the surgery, mice were retested to evaluate their olfactory and cognitive performance. Two weeks after the surgery, repetitive tail-tip blood sampling was undertaken (as described elsewhere) to assess the LH pulsatility profile." from WO2020221821A1 Patent Application.



Additional Highlights : Our Programmable iPRECIO minipumps used to administer humanized doses of antifungal. Journal of Antimicrobial Chemotherapy. **Intermittent micafungin for prophylaxis in a rat model of chronic *Candida albicans* gut colonization [first study to administer humanized doses of antifungal treatment to rats via implantable iPRECIO pumps]**

<https://academic.oup.com/jac/article-abstract/doi/10.1093/jac/dkaa243/5877001>.

Excerpt from publication: Pumps were pre-programmed to allow repeated infusion cycles of micafungin to simulate the expected systemic exposure of a human dose of 300mg every 72h or 55mg every 24h (Tables S1 and S2, available as Supplementary data at JAC Online).

Curious to learn more? Contact Primetech and ask us about trying out our IMS-200 Application Software <click here>

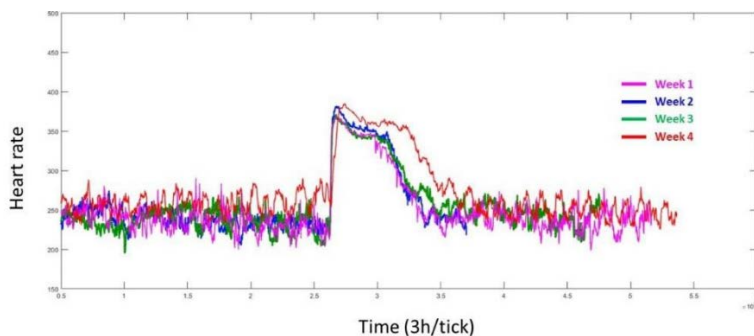
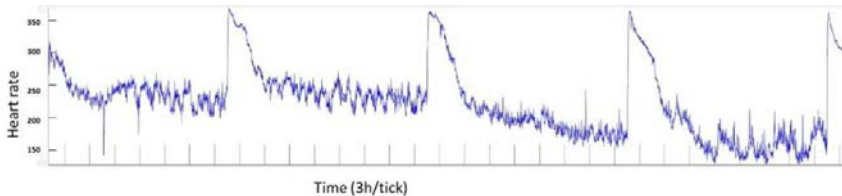
Mitochondrial ROS Drive Sudden Cardiac Death and Chronic Proteome Remodeling in Heart Failure

Circulation Research. 2018;CIRCRESAHA.118.312708,

<https://doi.org/10.1161/CIRCRESAHA.118.312708>

"The iPRECIO pump enables reliable, timed delivery of pharmacological agents. The pump was programmed for 1 hour delivery of Isoproterenol at 30ul/hr, total dose of 2mg/kg/day, once a day at the same time (1pm)"

Heart rate recordings over a period of 96 hours: showing internal consistency of iPrecio pumps Pumps inject isoproterenol once daily for a period of 1 hour. Heart rate recovers to baseline in 3-4 hours.



Figures credit Dey et al.

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

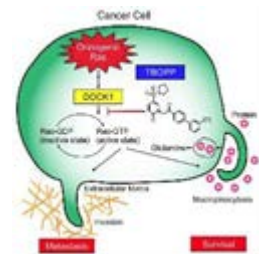
Convection-enhanced delivery of an anti-miR is well-tolerated, preserves anti-miR stability and causes efficient target de-repression: a proof of concept.

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>



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>
 Reproduced from Tajiri et al. (CC BY-NC-ND 4.0) without modification
<https://creativecommons.org/licenses/by-nc-nd/4.0/>



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>

iPRECIO Micro Infusion Pumps for Cancer Research

US20200330445A1 Continuous delivery of lenalidomide and other immunomodulatory agents [Open Access]

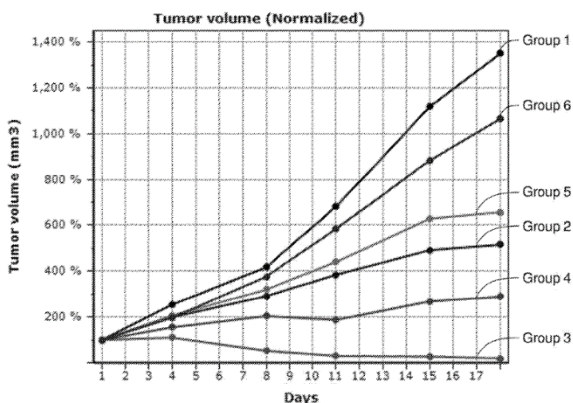
Marina BOROVIANSKAYA, Fotios PLAKOGIANNIS, Nisarg MODI, Tamanna LATHAR, Rod L. Hartwig, James C. OLIVER

See Example 1 <https://patents.google.com/patent/US20200330445A1/en?q=iprecio&q> or <https://lnkd.in/g/JdDA>

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 rates. 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://lnkd.in/g/cGAg4z> or <https://lnkd.in/g/JdDA>

"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 Borovinskaya et al. US 2020/0330445 A1

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

An adipokine feedback regulating diurnal food intake rhythms [Open Access]

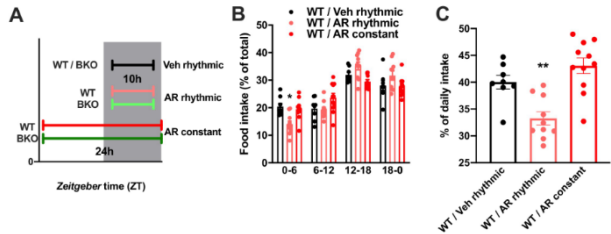
Tsang et al.

RESEARCH ARTICLE Jul 9, eLife 2020;9:e55388 DOI: 10.7554/eLife.55388 <https://lnkd.in/g/wXtMy>,

<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.

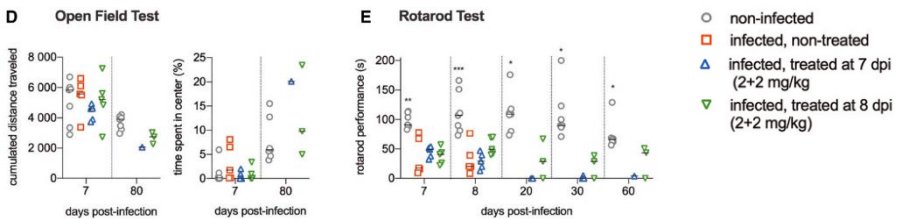
(A) Treatment regimen and groups. (B–D) Daily food intake profiles (B), relative light phase food intake (C) and total daily food intake



A combination of two human monoclonal antibodies cures symptomatic rabies [Open Access]

EMBO Mol Med (2020)e12628, <https://lnkd.in/g/qqtqvqD> *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)*

(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://lnkd.in/g/cbu3nc>

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

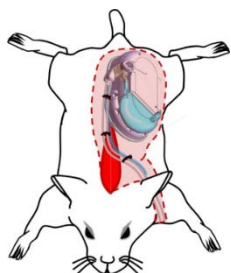
<https://www.jci.org/articles/view/83658> (Male mice, 8–12 weeks of age, 20–25 g, RoA-IV)

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

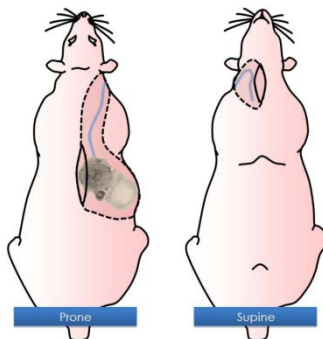
Vincent PREVOT Andrea MESSINA Paolo GIACOBINI Valérie LEYSEN Maria MANFREDI LOZANO (Down syndrome DS - Ts65Dn mice, RoA-SC) <https://patents.google.com/patent/WO2020221821A1/en?q=WO2020221821A1>

Example Pump implantation site and drug administration site

Intravenous Administration

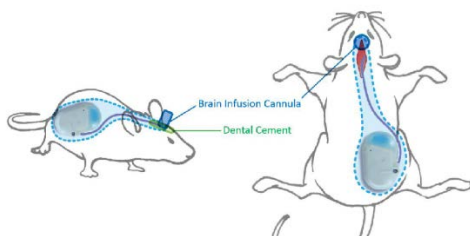


SMP-310R

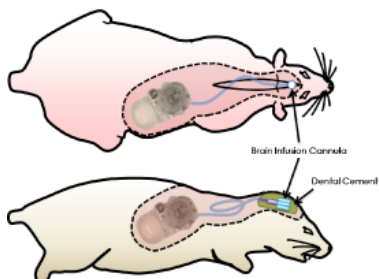


SMP-200

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/0B0pySJ1uXUqSVFBSVVAzTIZHaWc?resourcekey=0-kOMVOKHst22jjOxNE-5RyA&usp=sharing>



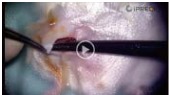
SMP-300 / SMP-310R with IP administration

<https://drive.google.com/drive/folders/0B0pySJ1uXUqSd1BNdDVZeEFQUWM?resourcekey=0-a8bb3m0lFMGYvBbFEp-w&usp=sharing>



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

<https://drive.google.com/drive/folders/0B0pySJ1uXUqSbENyQ21nY2REcHM?resourcekey=0-9HPwbMFKCRtX5G7IG7dUw&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-Uirh6Hx2Z0VIVpskbc7Tw&usp=sharing>



Refilling Video and Refiling FAQ

<https://drive.google.com/drive/folders/0B0pySJ1uXUqSX203d1I4bGsXOG8?resourcekey=0-OU5m2j7nCRxfhfJ4u3uSeA&usp=sharing>

Rat Surgeries (SMP-200)



Surgery Training Videos

<https://drive.google.com/drive/folders/0B0pySJ1uXUqSR2kzLVIMbWIRNUE?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.

Surgical Videos

From both Distributor and direct with Manufacturer (any way you want)

- Phone
- E-mail or fax
- Web meeting and training

iPRECIO® Key Features

- > Accurate patented Rotary Finger Method
 - Every pump is factory tested and calibrated
 - Better than $\pm 5\%$ 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 restraint (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.



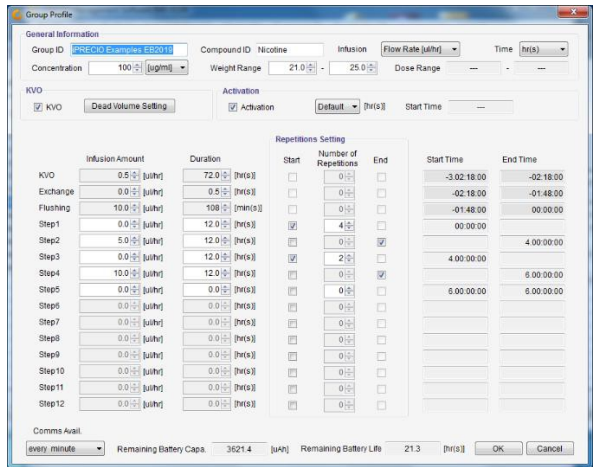
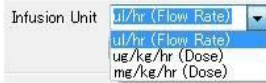
Precision

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 $\pm 5\%$.

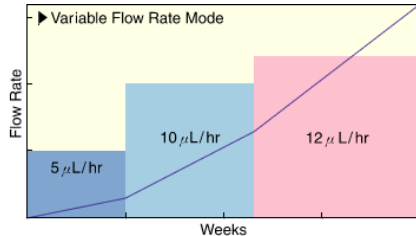
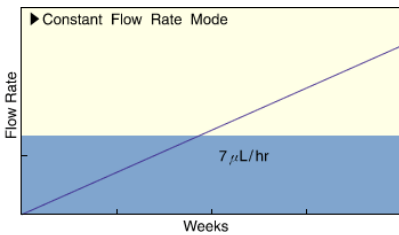
Programmable

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

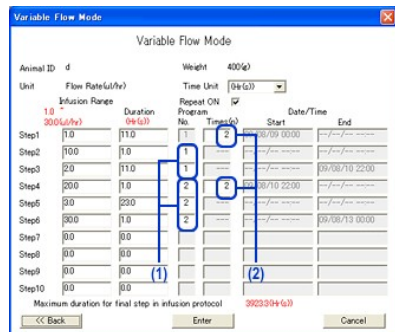
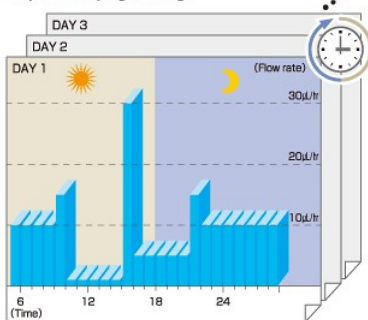
Each flow profile may contain up to 15 doses or flow rate steps. A single step would mean a fixed continuous dose or flow-rate for the study duration. A more complex infusion profile will contain more than 15 steps and may contain up to 15 steps. KVO and dead volume flushing functions may be programmed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



Repeat Mode program image



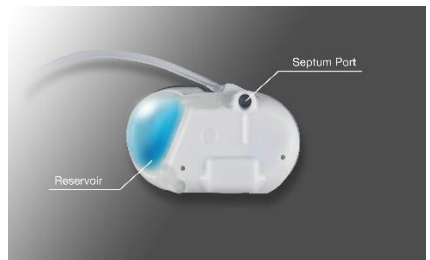
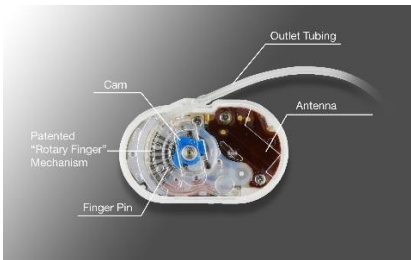
iPRECIO[®] is an Ultimate Choice

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.

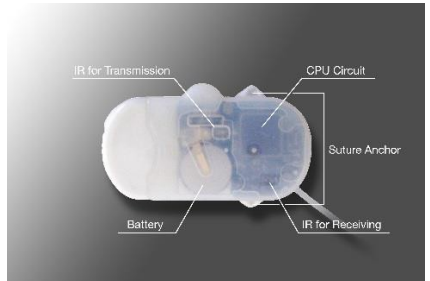
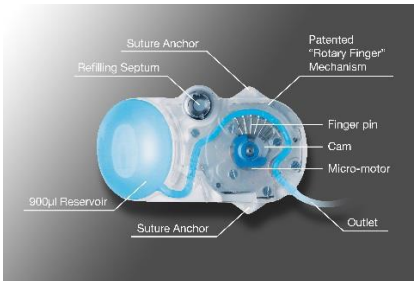


iPRECIO[®] Pump's Structure

> 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.

> SMP-200



iPRECIO® Management System consists of:

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

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 : $\mu\text{L/hr}$

* 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 $\mu\text{L/hr}$	196 hr	1 week	5.8 ml
19.0 $\mu\text{L/hr}$	307 hr	1.8 weeks	5.8 ml
8.5 $\mu\text{L/hr}$	669 hr	1 month	5.6 ml
1.0 $\mu\text{L/hr}$	4,328 hr	6 months	4.3 ml

Model	SMP-310R IMS-310R (new!!)	SMP-300 IMS-300 (discontinued)	SMP-200 IMS-200
Appearance of the pump	 24.8(L) x 15.0(W) x 7.2 (H) mm, Max. height 7.5mm	 24.8(L) x 15.0(W) x 7.2 (H) mm, Max. height 7.4mm	 38.7 (L) X 19.2 (W) X 9.7 (H) mm
Type	Implantable SC	Implantable SC	Implantable SC
Volume / Weight	2.26cc / 3.4g	2.15cc / 3.3g	7.20cc / 7.9g
Animal Species	Mouse or larger	Mouse or larger	Rats or larger
Reservoir Volume	130 μ L	130 μ L	900 μ L
Flow Rate (Setting Resolution)	0.0 – 10.0 μ L/hr (0.1 μ L/hr)	0.0 – 10.0 μ L/hr (0.1 μ L/hr)	0.0, 0.2, 0.5&1.0 – 30.0 μ L/hr (0.1 μ L/hr)
Flow Steps / Repeat	15 / Yes	15 / Yes	10 / Yes
Battery Life	0 & 0.1 μ L/hour 67 days 1 μ L/hour up to 41 days 10 μ L/hour up to 8 days	0 & 0.1 μ L/hour 46 days 1 μ L/hour up to 33 days 10 μ L/hour up to 9 days	0, 0.2, 0.5, 1 μ L/hour - 6 mths 2.5 μ L/hour - 86 days 30 μ L/hour - 8 days
Programmable	Wireless Preprogrammable	Wireless Preprogrammable	Preprogrammed prior to implantation
Wireless Distance	1 – 6m	< 1m	-
Communication Availability	1m, 1h, 2h, 4h, 6h, 12h, 24h and NONE (8 choices)	1m, 2h, 6h, 24h and None (4 choices)	-

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 (\leq 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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