

Drug dosing regimens influence outcomes.

Application Examples

from peer reviewed publications and webinars

More translational preclinical models

Micro infusion pump



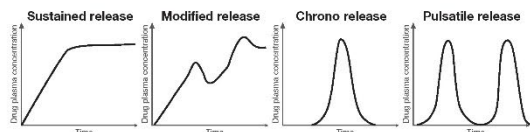
Implantable, Programmable and Refillable



SMP-200
1ul/hr 6months



SMP-310R
0.1ul/hr. 67.8days



All things mouse Pg.22, 28 & 31

Cardiovascular Pg.13 & 28-30

Clinical Regimens Pg.32

GLP & Toxicology Pg.18

Neuroscience Pg.9-12, 15, 17, 23-27

Metabolism Pg.5-8

Oncology Pg.14, 16 & 19-23

Webinars Pg.19-20, 27

Micro infusion pump

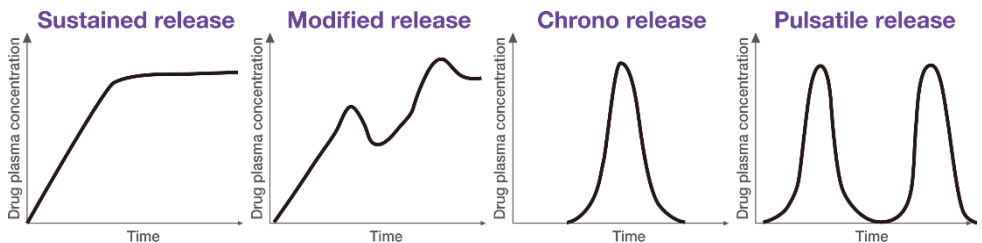


Implantable, Programmable and Refillable

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 :

" 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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 Program what you need for overcoming:-
 - a. Narrow therapeutic index
 - i. Maximizing efficacy with timed infusion
 - ii. 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

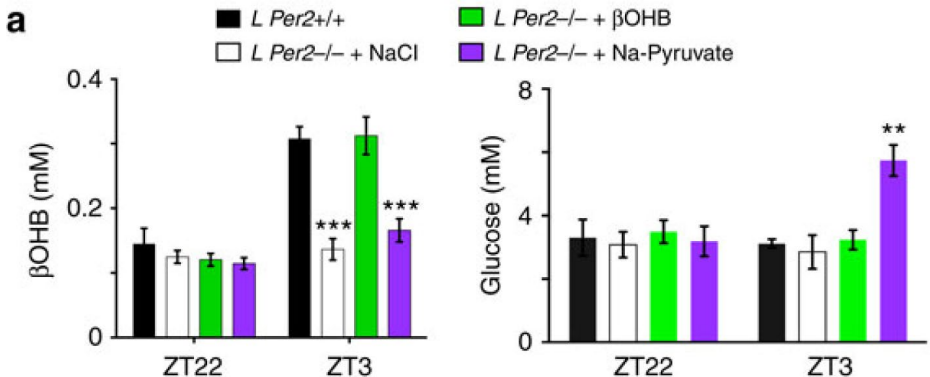


Figure 1 (Figure 4a in Full Article) **Rescue of food anticipation in *L Per2*^{-/-} mice by β -hydroxybutyrate.** (a) Timed release of β OHB (green) but not NaCl (white) or Na-Pyruvate (purple) in *L Per2*^{-/-} mice mimics the β OHB levels in plasma of *L Per2*^{+/+} control animals (black). Measured 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

[https://www.jlr.org/article/S0022-2275\(20\)35497-3/fulltext](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>

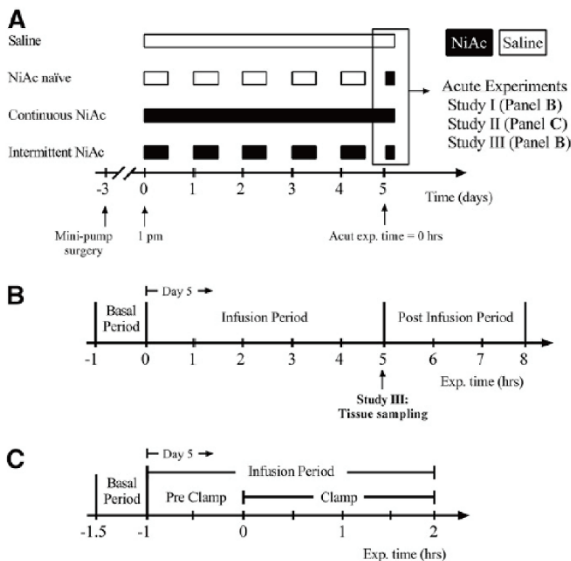


Fig. 2 (Figure 1 in Kroon et al.)

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-isoglycemic clamps).

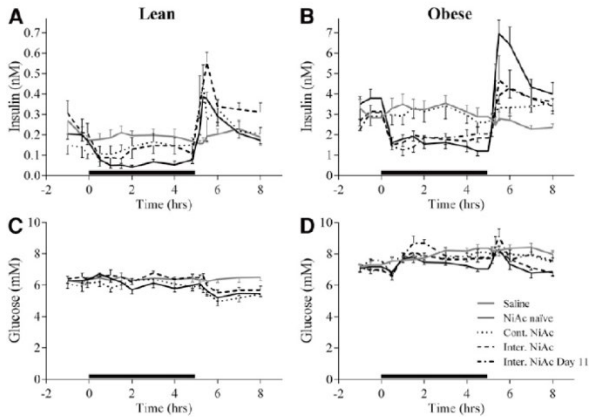


Fig. 3. (Figure 5 in Kroon et al.) Plasma insulin (A, B) and glucose (C, D) concentration in lean (left) and obese (right) following infusion of saline (lean $n = 5$, obese $n = 12$) or NiAc ($0.17 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) given acutely (NiAc naïve, $n = 7/\text{group}$)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

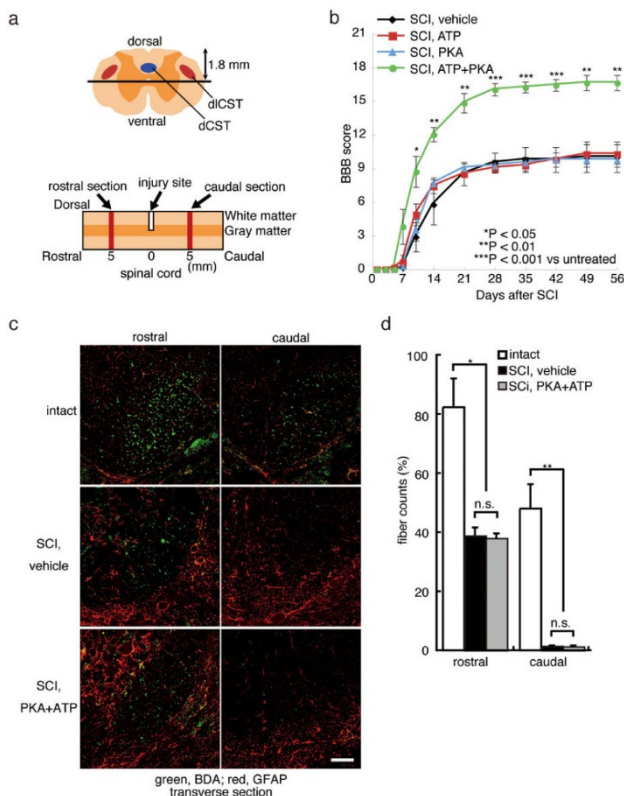


Figure 4 (Figure 1 from Suehiro et al)

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 (dLST) 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 μ m. (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>

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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

[https://doc.primetech.co.jp/hubfs/iPRECIO/Envigo_Pharma_Dils_14.4.4_\(intrathecal-recathco\).pdf](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 Life Sciences 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;

<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 $30 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$. 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>

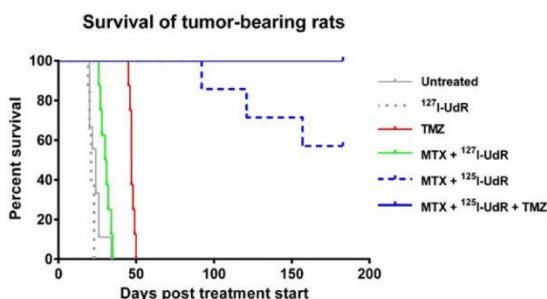


Figure 6. Kaplan-Meier plot showing that the survival benefit of neoadjuvant MTX + ¹²⁵I-UdR as stand-alone Auger-therapy (group4) or with concomitant, systemic TMZ chemotherapy (group5) was highly significant compared with the non-radioactive, but chemically identical treatment MTX + ¹²⁷I-UdR (group3,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

"Pumps were programmed to run with a flow rate of 0.2 $\mu\text{L/h}$ 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.

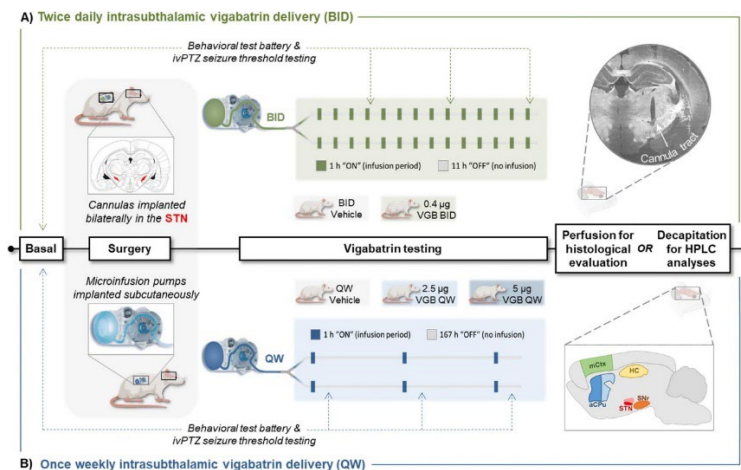
Chronic intermittent convection-enhanced delivery of vigabatrin to the bilateral subthalamic nucleus in an acute rat seizure model. [Open Access]

Epilepsy Research 199 (2024): 107276.

<https://www.sciencedirect.com/science/article/pii/S0920121123000212>

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Keywords: Basal ganglia Epilepsy GABA transaminase Intracerebral pharmacotherapy Pentylentetrazole 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 μ L/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 μ L/h). The pump was refilled every 24 h with a study duration of 5 days.

An, Le, et al.

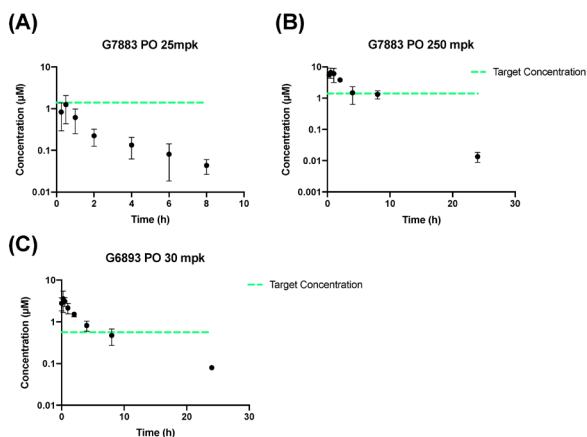
Early Stage Preclinical Formulation Strategies to Alter the Pharmacokinetic Profile of Two Small Molecule Therapeutics. [Open Access]

Epilepsy Research 199 (2024): 107276.

Pharmaceuticals 17.2 (2024): 179. <https://www.mdpi.com/1424-8247/17/2/179>

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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.

Corticosterone Pumps

Pumps were programmed in 24 h repetitive loops to deliver corticosterone at 4 $\mu\text{L/h}$ from ZT6-ZT10, 6 $\mu\text{L/h}$ from ZT10-16, 4 $\mu\text{L/h}$ from ZT16-ZT18 and a maintenance dose of 1 $\mu\text{L/h}$ 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

A rhythm in stress hormone (corticosterone) is reestablished in SCN-lesioned rats by use of programmable micropumps

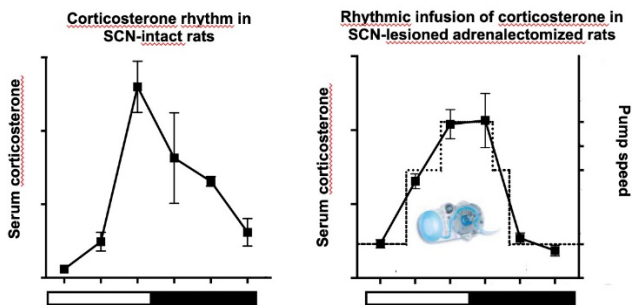


Figure kindly provided by Dr. T Bering.

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

The use of th

Infusion Pump in Ambulatory

Cardiovascular Dog Studies

DSI East Coast User Group

Meeting, Philadelphia, PA, U

States October 29th and 30th 201

Use of iPRECIO implantable micro infusion

4th Infusion Technology Organization Meeting, May 8th-9th 2014

Validation and use of the iPRECIO® M

Society of Toxicology Annual Meeting, San Francisco, United States.

March 11th to 14th 2012.



The Use of the Iprecio Dual Infusion Pump in Ambulatory Cardiovascular Dog Studies

Laura Ringer
Pfizer

Team Members: Peter Harris, Vincent Bernardo

 WORLDWIDE RESEARCH & DEVELOPMENT
Drug Safety R&D

Validation and use of the iPreBio[®] micro-infusion pump on GLP studies
 J. Poirier, F. Frenette, G. Gosselin
 Charles River Laboratories Preclinical Services Montreal Inc., 22022 Transcanadienne, Dorvalville, Quebec, Canada H9X 3T0

charles river
 laboratories imaging, genomics, safety

Introduction

Low infusion rates are generally required for conduct of preclinical studies using non-intrinsically routes of administration such as intraperitoneal, intracerebral or subcutaneous infusion or possibly other larger tissue infusion. Achieving these rates of infusion with standard infusion pumps can present some difficulties, and the use of a micro-infusion pump is required to ensure accurate and precise infusion rates, and to avoid overdosing or underdosing. The iPreBio[®] micro-infusion pump is an integrated, programmable micro-infusion pump, the iPreBio[®] micro-infusion pump, and is indicated for accuracy of delivery for possible use in regularly control studies requiring very low infusion rates.

Material and Methods

Micro infusion pump

The iPreBio[®] micro infusion pump is indicated to allow infusion at rates of 1 to 10 $\mu\text{L/hr}$, with up to 4 containers of syringes. This allows flexibility in programming, permitting the use of either 0.5 mL or 1 mL syringes (not shown), and the programming of the pump to deliver a specific volume of fluid over a specific time period between two infusions, such as during a competition.

Flow rate	Flow rate error	Flow rate accuracy
1.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±5.0%
2.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±2.5%
3.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±1.7%
4.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±1.3%
5.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±1.0%
6.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.8%
7.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.7%
8.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.6%
9.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.6%
10.0 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.5%

The stability of the pump is dependent of the size of infusion, and is determined by the manufacturer to be as follows:

Flow rate	1.0 $\mu\text{L/hr}$	2.0 $\mu\text{L/hr}$	3.0 $\mu\text{L/hr}$	4.0 $\mu\text{L/hr}$	5.0 $\mu\text{L/hr}$	6.0 $\mu\text{L/hr}$	7.0 $\mu\text{L/hr}$	8.0 $\mu\text{L/hr}$	9.0 $\mu\text{L/hr}$	10.0 $\mu\text{L/hr}$
Stability	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$	±0.05 $\mu\text{L/hr}$

The iPreBio[®] micro infusion pump is equipped with an on-board silicon chip, which may be required on other types of infusion depending on the route of administration. The pump is surgically implanted subcutaneously, and is connected to the animal via a catheter. The pump is implanted in the animal's back, and is connected to the animal's back via a catheter. The pump is implanted in the animal's back, and is connected to the animal's back via a catheter. The pump is implanted in the animal's back, and is connected to the animal's back via a catheter.

Pump delivery accuracy

The iPreBio[®] pump was extensively tested and the accuracy of the delivery of the micro-infusion pump was evaluated in order to be able to use the pump in a variety of animal studies. These studies were performed with a 0.5 mL syringe, and the pump was able to deliver a volume of fluid with an accuracy of delivery of 1.0 $\mu\text{L/hr}$ to 10.0 $\mu\text{L/hr}$ with an accuracy of $\pm 0.05 \mu\text{L/hr}$ (see table below). The pump was able to deliver a volume of fluid with an accuracy of $\pm 0.05 \mu\text{L/hr}$ (see table below).

Results and Conclusion

Percent recoveries were calculated and are presented below:

Flow rate	Actual flow rate	Recovery	Flow rate	Actual flow rate	Recovery
1.0 $\mu\text{L/hr}$	1.0 $\mu\text{L/hr}$	100.0%	1.0 $\mu\text{L/hr}$	1.0 $\mu\text{L/hr}$	100.0%
2.0 $\mu\text{L/hr}$	2.0 $\mu\text{L/hr}$	100.0%	2.0 $\mu\text{L/hr}$	2.0 $\mu\text{L/hr}$	100.0%
3.0 $\mu\text{L/hr}$	3.0 $\mu\text{L/hr}$	100.0%	3.0 $\mu\text{L/hr}$	3.0 $\mu\text{L/hr}$	100.0%
4.0 $\mu\text{L/hr}$	4.0 $\mu\text{L/hr}$	100.0%	4.0 $\mu\text{L/hr}$	4.0 $\mu\text{L/hr}$	100.0%
5.0 $\mu\text{L/hr}$	5.0 $\mu\text{L/hr}$	100.0%	5.0 $\mu\text{L/hr}$	5.0 $\mu\text{L/hr}$	100.0%
6.0 $\mu\text{L/hr}$	6.0 $\mu\text{L/hr}$	100.0%	6.0 $\mu\text{L/hr}$	6.0 $\mu\text{L/hr}$	100.0%
7.0 $\mu\text{L/hr}$	7.0 $\mu\text{L/hr}$	100.0%	7.0 $\mu\text{L/hr}$	7.0 $\mu\text{L/hr}$	100.0%
8.0 $\mu\text{L/hr}$	8.0 $\mu\text{L/hr}$	100.0%	8.0 $\mu\text{L/hr}$	8.0 $\mu\text{L/hr}$	100.0%
9.0 $\mu\text{L/hr}$	9.0 $\mu\text{L/hr}$	100.0%	9.0 $\mu\text{L/hr}$	9.0 $\mu\text{L/hr}$	100.0%
10.0 $\mu\text{L/hr}$	10.0 $\mu\text{L/hr}$	100.0%	10.0 $\mu\text{L/hr}$	10.0 $\mu\text{L/hr}$	100.0%

As the volumes of delivery were at times small, the accuracy of delivery was evaluated for calculation of the concentration of infusion solution achieved. Infusion solutions of 1 mL containing 10.0 μL of saline (NaCl) were the volume taken (NaCl = 10.0 μL). The delivery concentration was determined using a Molecular 1000 instrument.

In conclusion, the iPreBio[®] micro-infusion pump is suitable to be used in a variety of animal studies, and is suitable for use in regularly control studies when very low rates of infusion are required.

References

M. J. L. M. VAN DER MEULEN, H. A. J. M. VAN DIJK, F. C. M. DE VRIES

Fukutaro Mizuhashi

Physiological conc

Fundamental Toxicological Sciences Vol.3 (2016) No.1 p.

https://www.jstage.jst.go.jp/article/fts/3/1/3_1/_article

Webinar

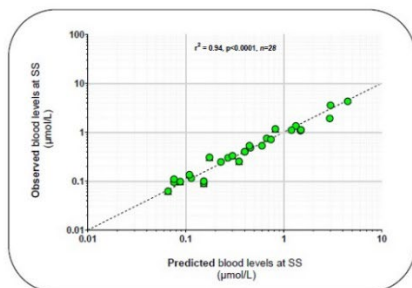
Webinar: Compound Delivery, PK-PD & Validation Studies in Oncology Studies

Christian Schnell, Associate Director Oncology NIBR Novartis in Basel

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

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)

↳ $r^2 = 0.94, p < 0.0001, n = 28$

28 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)

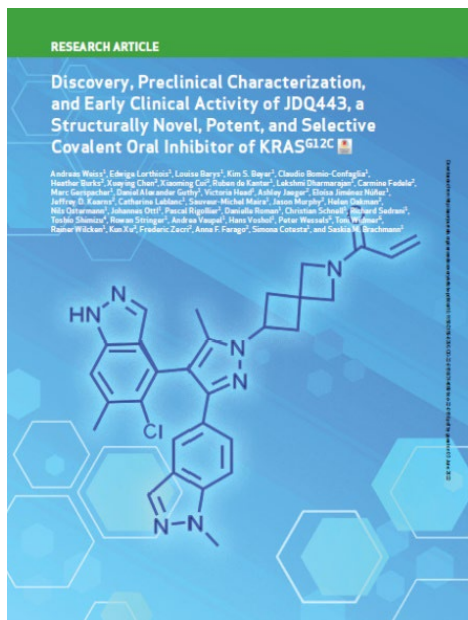
Related Reference.

Weiss, Andreas, et al. "Discovery, Preclinical Characterization, and Early Clinical Activity of JDQ443, a Structurally Novel, Potent, and Selective Covalent Oral Inhibitor of 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 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. "excerpt

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

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>

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)

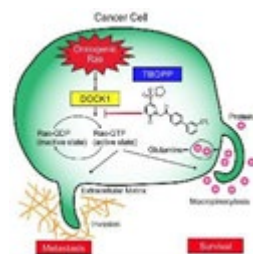
Targeting Ras-Driven Cancer Cell Survival and Invasion through Selective Inhibition of DOCK 1

Cell Reports 19, 969-980, May 2, 2017

<http://dx.doi.org/10.1016/j.celrep.2017.04.016>

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<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>

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

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

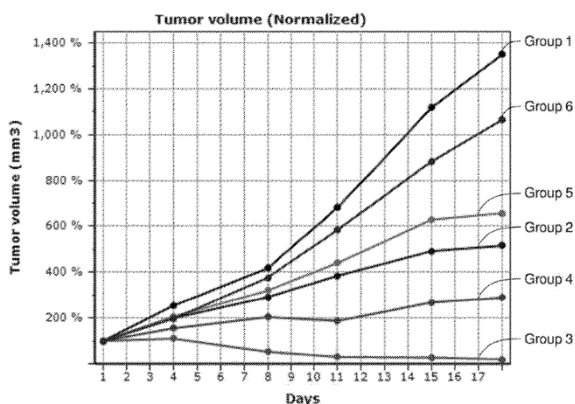
Video (<https://youtu.be/d8CHR7et5zs> or <https://www.linkedin.com/feed/update/urn:li:activity:6768444633161842688>) from Start to 7 minutes. Rodent Studies of PK, Safety and Tolerability of LLD in Healthy and SCID Mice by Jamie Oliver Chief Medical Officer Starton Therapeutics.

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 Borovinskaya 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

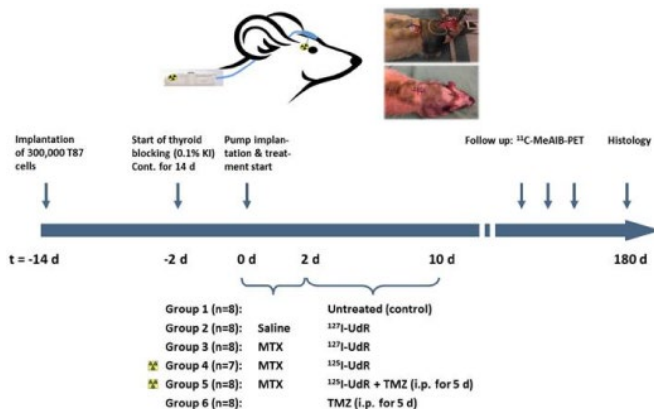


Figure 1 reproduced from Thisgaard et al. (CC BY-NC-ND 4.0)

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

<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

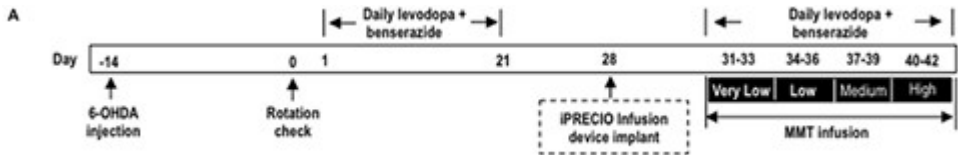


Figure 1A reproduced without modification from doi.: 10.3389/fneur.2019.01258.

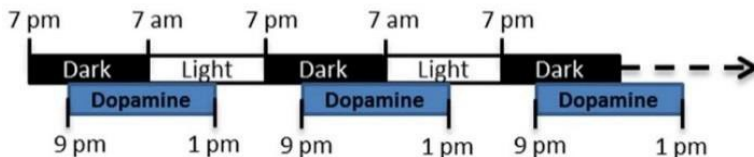
Attribution 4.0 International (CC BY 4.0) <https://creativecommons.org/licenses/by/4.0/>

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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[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)

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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

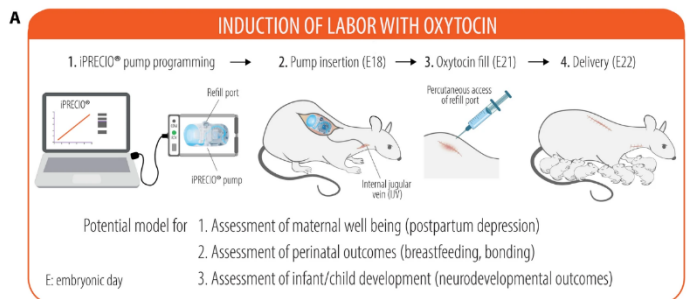
PNAS July 10, 2018 115 (28) 7254-7259; <https://doi.org/10.1073/pnas.1804372115>

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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New Horizons: Gonadotropin-Releasing Hormone and Cognition

Vincent Prevot, PhD

Lille Neuroscience & Cognition, Inserm

"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_bmc_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]

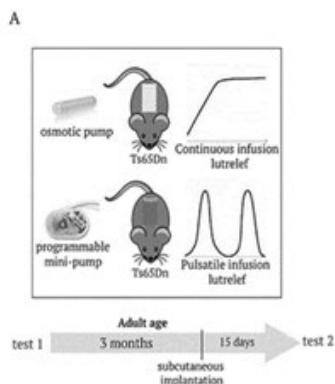
Vincent PREVOT Andrea MESSINA Paolo GIACOBINI

Valérie LEYSEN Maria MANFREDI LOZANO

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



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.”

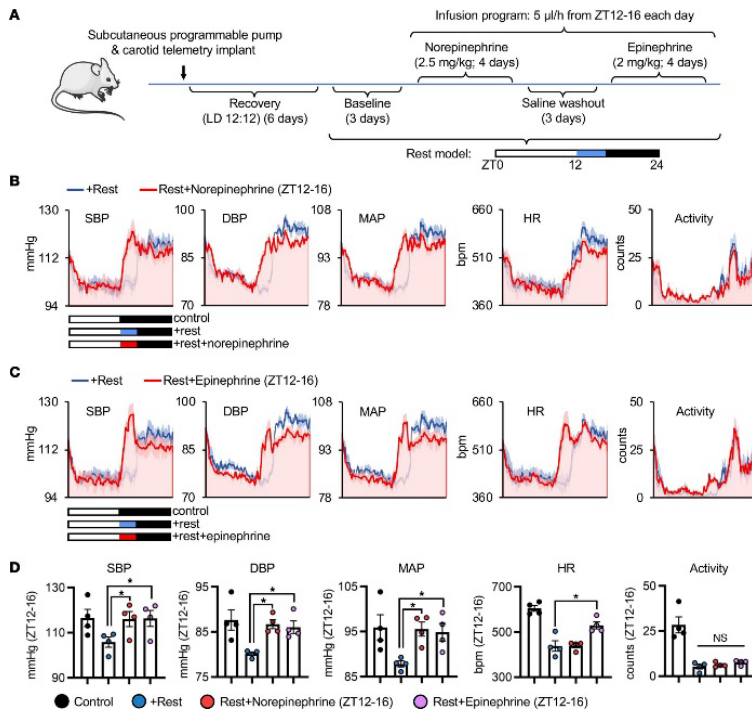


Figure 6. A brief period of morning rest delays the onset of sympathetic activity to benefit cardiovascular hemodynamics. (A) Schematic of experimental design. Healthy mice were implanted with both a subcutaneous programmable iPRECIO infusion pump and carotid artery radiotelemetry. For full details see 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>

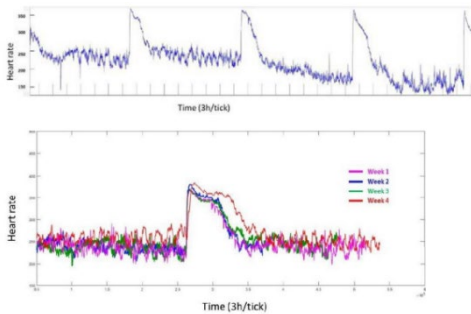
Published in Volume 7, Issue 22 on November 22, 2022

© 2022 Reitz et al. This work is licensed under the Creative Commons Attribution 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

"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>

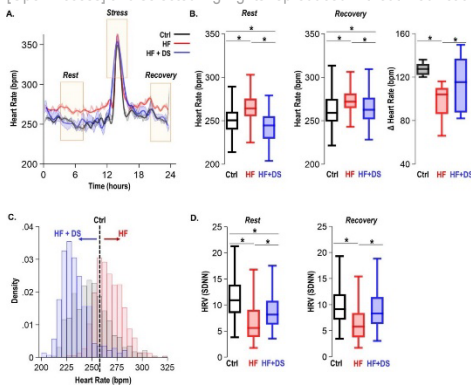


The animal model used in this research involved guinea pigs subjected to ascending aortic constriction (AC) and daily administration of isoproterenol via a programmable iPRECIO pump. This model simulates heart failure and sudden cardiac death, progressing from compensated hypertrophy to heart failure 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>

ATtribution 4.0 International <https://creativecommons.org/licenses/by/4.0/>

[Open Access] and selected highlights reproduced without modification under Creative Commons CC-BY license.

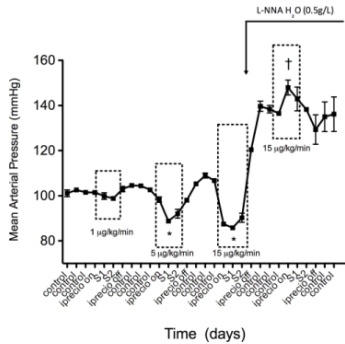


Dantrolene treatment decreases heart rate and improves chronotropic competency in heart failure (HF). (A) Plot shows heart rate derived from 24 hr continuous electrocardiogram (ECG) recordings. The animals were subjected to mild transient β -AR stress for 1 hr. Continuous ECG analysis was performed at 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.

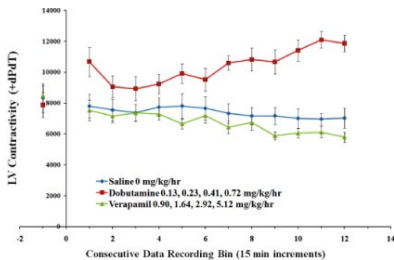
iPRECIO® Micro Infusion Pump:

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.

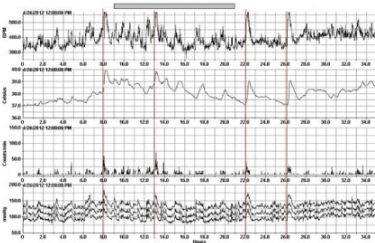
iPRECIO® Micro Infusion Pump:

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 Physiology Jul 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]

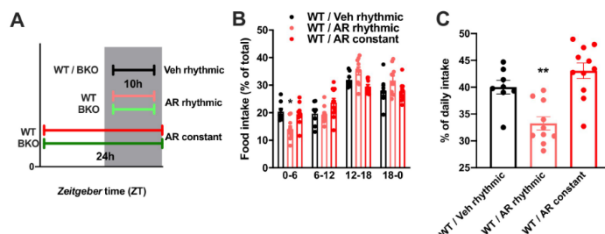
Tsang et al.

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.

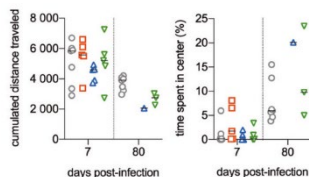
(A) Treatment regimen and groups. (B–D) Daily food intake profiles (B), relative light phase food intake (C) and total daily food intake



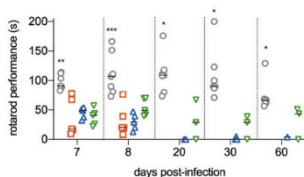
A combination of two human monoclonal antibodies cures symptomatic rabies [Open Access]

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)*

D Open Field Test



E Rotarod Test



○ non-infected
□ infected, non-treated
△ infected, treated at 7 dpi (2+2 mg/kg)
▽ infected, treated at 8 dpi (2+2 mg/kg)

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 $\alpha 7$ nAChR+ 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 micafungin 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](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

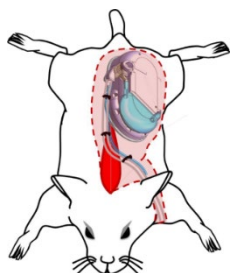
Hot off the press: Dose regimens.

"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."

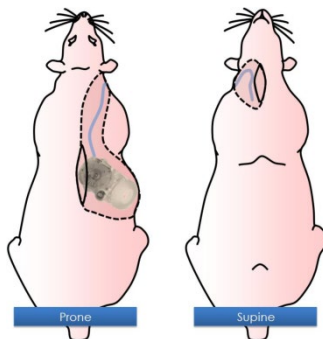
Withey, Sarah L., Jack Bergman, and Carol A. Paronis. **"The effects of chronic naltrexone on reinstatement of opioid-induced drug-seeking behavior and antinociception."** Journal of Pharmacology and Experimental Therapeutics 389.1 (2024): 5-14. <https://jpet.aspetjournals.org/content/389/1/5.abstract>

Example Pump implantation site and drug administration site

Intravenous Administration

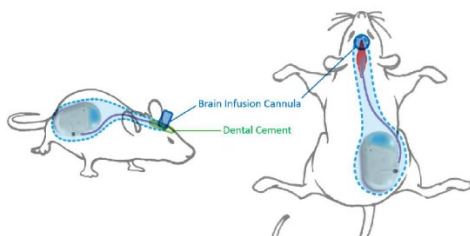


SMP-310R

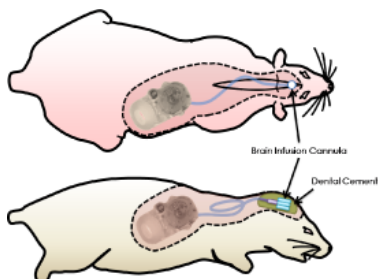


SMP-200

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/0B0pySJ1uXUqSVFBSVVaZTIZHaWc?resourcekey=0-kOMVOKHst22jiOxNE-5RyA&usp=sharing>



SMP-300 / SMP-310R with IP administration

<https://drive.google.com/drive/folders/0B0pySJ1uXUqSd1BNdDVZeEFQUWM?resourcekey=0-a8bb3m0lFMGZYvBbfEp-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/0B0pySJ1uXUqSdIFtVfJdJMFfncWM?resourcekey=0-GMNTGvE5ZXG9j0qS_QPNAw&usp=sharing



SMP-300 / SMP-310R with ICV administration

<https://drive.google.com/drive/folders/0B0pySJ1uXUqSUGxHWkdLTXMwSEk?resourcekey=0-Uirh6Hx2Z0VIVpskbca7Tw&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/0B0pySJ1uXUqSR2kzLVIMbWtRNUe?resourcekey=0-2iWx-iiDd7sJPI2AZIV4A&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 $\pm 5\%$ 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 1 step and may contain up to 15 steps. KVO and dead volume flushing functions may be programmed within the 15 programmable steps.

Group Profile

General Information
 Group ID: iPRECIO Examples E000111 Compound ID: Nicotine Infusion: Flow Rate (ul/hr) Time: (hrs)
 Concentration: 100.0 (µg/ml) Weight Range: 21.0 (g) - 25.0 (g) Dose Range: ---

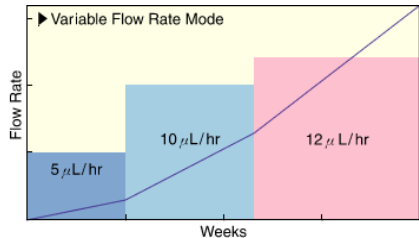
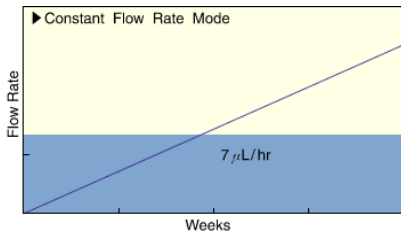
KVO: ☒ KVO Activation: ☒ Activation Default: (hrs) Start Time: ---

Repetitions Setting

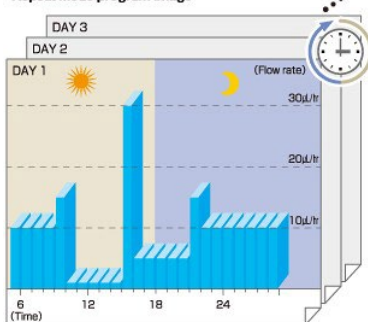
KVO	Infusion Amount	Duration	Start	Number of Repetitions	End	Start Time	End Time
KVO	0.5 (ul/hr)	72.0 (hrs)	☐	0 (1)	☐	-3:02:18.00	-02:18:00
Exchange	0.0 (ul/hr)	0.5 (hrs)	☐	0 (1)	☐	-02:18:00	-01:48:00
Flushing	10.0 (ul/hr)	108 (mins)	☐	0 (1)	☐	-01:48:00	00:00:00
Step1	0.0 (ul/hr)	12.0 (hrs)	☒	4 (1)	☐	00:00:00	
Step2	5.0 (ul/hr)	12.0 (hrs)	☐	0 (1)	☒		4:00:00:00
Step3	0.0 (ul/hr)	12.0 (hrs)	☒	2 (1)	☐	4:00:00:00	
Step4	10.0 (ul/hr)	12.0 (hrs)	☐	0 (1)	☒		6:00:00:00
Step5	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐	6:00:00:00	6:00:00:00
Step6	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐		
Step7	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐		
Step8	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐		
Step9	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐		
Step10	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐		
Step11	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐		
Step12	0.0 (ul/hr)	0.0 (hrs)	☐	0 (1)	☐		

Comments Avail: every minute Remaining Battery Caps: 3621.4 (µA) Remaining Battery Life: 21.3 (hrs) OK Cancel

> **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



Variable Flow Mode

Variable Flow Mode

Animal ID: d Weight: 400(g)

Unit: Flow Rate (ul/hr) Time Unit: (hr:min)

Infusion Range: 1.0 - 30.0 (ul/hr)

Step	Unit	Flow Rate (ul/hr)	Duration (hrs:min)	Repeat ON Program	Start Date/Time	End Date/Time
Step1	1.0	1.0	1:0	☒	26/09/2000	
Step2	10.0	1.0	1:0	☒		
Step3	2.0	1.0	1:0	☒	09/08/2000	22:00
Step4	1.0	1.0	1:0	☒	26/10/2000	22:00
Step5	3.0	2.0	2:0	☒		
Step6	3.0	1.0	2:0	☒		
Step7	0.0	0.0	0:0	☐		
Step8	0.0	0.0	0:0	☐		
Step9	0.0	0.0	0:0	☐		
Step10	0.0	0.0	0:0	☐		

Maximum duration for final step in infusion protocol: 3923:394 (s)

<< Back Enter Cancel

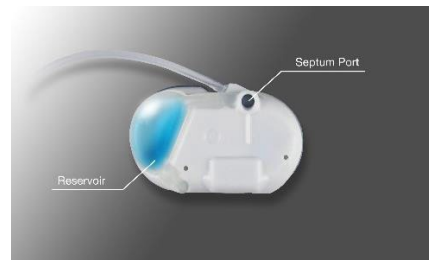
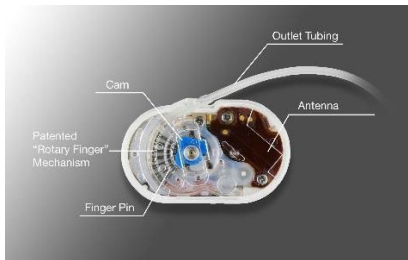
iPRECIO® is an Ultimate Choice

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.

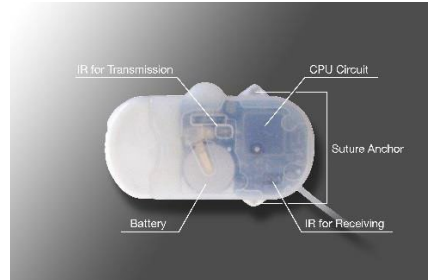
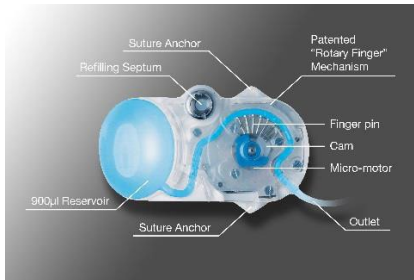


iPRECIO® Pump's Structure

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

* 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	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 μ L	900 μ L
Flow Rate (Setting Resolution)	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	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, 0.2, 0.5, 1 μ L/hour - 6 mths 2.5 μ L/hour - 86 days 30 μ L/hour - 8 days
Programmable	Wireless Preprogrammable	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 ($\leq$ 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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