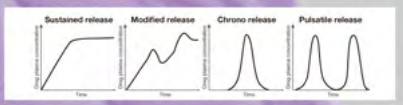
# **Micro** infusion pump

# iPRECIO®

Implantable, Programmable and Refillable

# Application Examples

## from peer reviewed publications




**Elevate the best New Molecular Entity (NME) and New Chemical Entity (NCE) to the preclinical stage with the highest probability of successfully reaching the marketplace.**

With a wide range of compatible solvents and vehicles, iPRECIO Micro Infusion Pumps are used as a platform in-vivo technology to:-

- Evaluate both non-optimized and optimized compounds.
- Maximize the information content about target engagement. (PK/PD)
- Minimize confounding variables due to stress and human interactions.
- Simulate humanized exposure profiles for translational research.

# Micro infusion pump

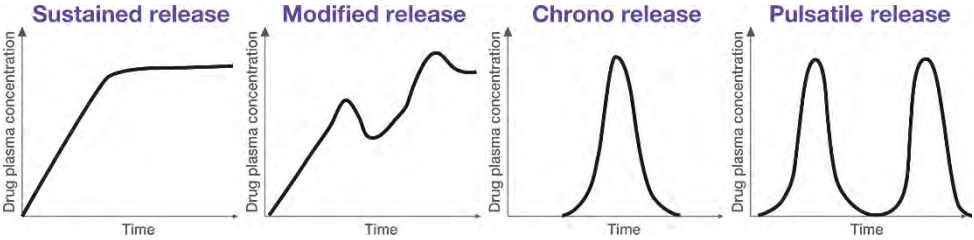
iPRECIO®

Implantable, Programmable and Refillable

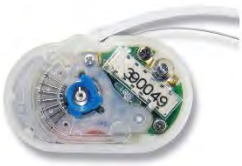
## iPRECIO Micro Infusion Pumps

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

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




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




SMP-300


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.*

# Contents

# Research Applications 1

SC Administration

Timed release of Test Article (TA), ßOHB

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

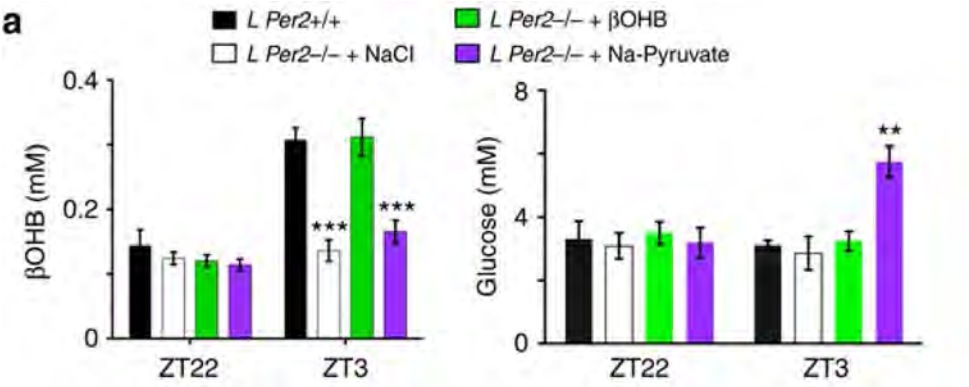



Figure 1 (Figure 4a in Full Article) **Rescue of food anticipation in L Per2$^{-/-}$mice by ß-hydroxybutyrate**. (a) Timed release of ßOHB (green) but not NaCl (white) or Na-Pyruvate (purple) in L Per2$^{-/-}$ mice mimics the ßOHB levels in plasma of L Per2$^{+/+}$ control animals (black). Measured after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



**Purpose of the study:**

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

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

**Short methods or use of the pumps:**

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

**Results/significance:**

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

**Research Need:**

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

**Additional information on mini-pump implant**

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

**Related Circadian rhythm Research using iPRECIO SMP-200 in mice**

In vivo imaging of clock gene expression in multiple tissues of freely moving mice
Nature Communications 7, Article number: 11705 doi:10.1038/ncomms11705
https://www.nature.com/articles/ncomms11705

# Research Applications 2

SC Administration

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

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

Tobias Kroon, Ann Kjellstedt, Pia Thalén, Johan Gabrielsson, Nicholas D. Oakes
**Dosing Profile Profoundly Influences Nicotinic Acid's Ability to Improve Metabolic Control in Rats**
The Journal of Lipid Research, doi: 10.1194/jlr.M058149 , July 13, 2015
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

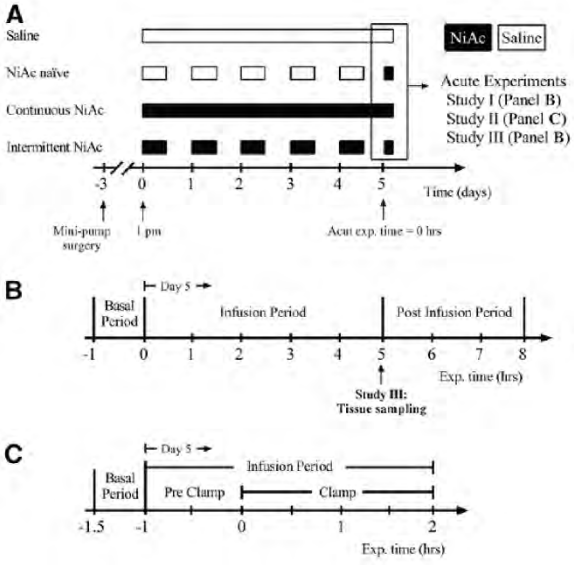



Fig. 2 (Figure 1 in Kroon et al.)
A: NiAc and saline infusion profiles across studies I–III.
Black (NiAc) and open (saline) bars represent time periods of constant rate infusions during days 1–5. B: Terminal protocol for studies I (NiAc-induced FFA lowering) and III (NiAc-induced changes in adipose tissue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

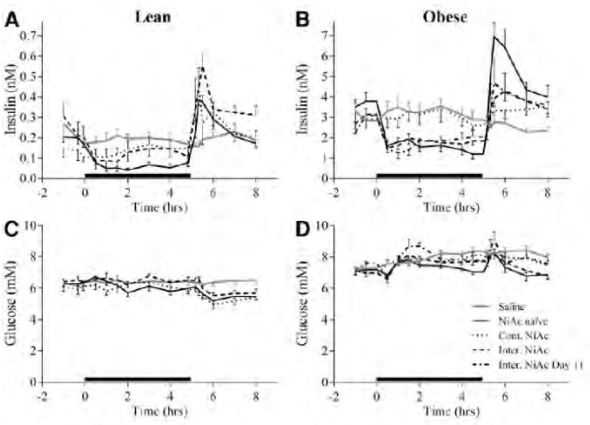



Fig. 3. (Figure 5 in Kroon et al.) Plasma insulin (A, B) and glucose (C, D) concentration in lean (left) and obese (right) following infusion of saline (lean n = 5, obese n = 12) or NiAc (0.17µmol·min -1·kg -1 ) given acutely (NiAc naïve, n = 7/group) or following 5 days continuous (Cont. NiAc, lean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



**Purpose of the study:**

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

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

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

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

**iPRECIO SMP-200 pumps were programmed to deliver the required exposure profiles of N icotinic A cid t o s tudy impact o n t olerance d evelopment ( see f igure 2A) an d attenuate the FFA rebound development respectively (not shown)**

**Results/significance:**

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

**Research Need:**

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

# Research Applications 3

**Intrathecal Administration**

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

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

**Ecto-domain phosphorylation promotes functional recovery from spinal cord injury**

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

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

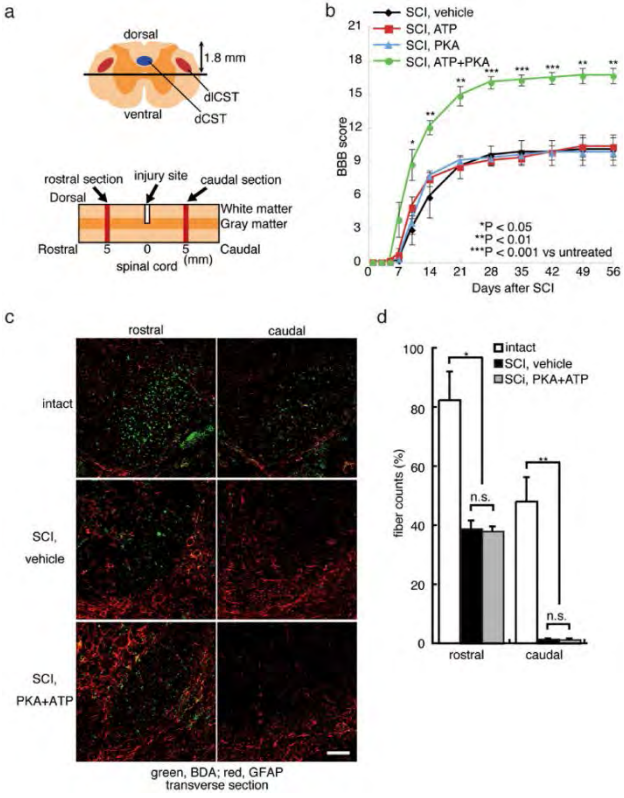



Figure 4 (Figure 1 from Suehiro et al)

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

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

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

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

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

## Related publication examples: Refilling to Improve Test Article Stability

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

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

# Research Applications 4

Intrathecal Administration

Excerpt from Mitchell et al. Full reference in box.

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

Mitchell D., Read, K., Chapman M. and Patten D.
**Intrathecal administration using the iPRECIO® implanted pump**
Development in Life Sciences, Vol 14, No. 4
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 $\mu g \cdot kg^{-1} \cdot day^{-1}$ in a solution of 15% ethanol,
50% DMSO, and 35% water at a concentration of 10 mg aldosterone/ml.

**Enhanced Resistance to Permeability Transition in Interfibrillar Cardiac Mitochondria in Dogs: Effects of Aging and Long Term Aldosterone Infusion.**
Am J Physiol Heart Circ Physiol ajpheart.00674.2012;
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 $\mu g \cdot kg^{-1} \cdot day^{-1}$ The pump reservoir was 900 µl and was refilled percutaneously every 20–30 days through an injection port on the pump. The pump reservoir was evacuated before refilling to ensure the pump had properly discharged its contents and was then refilled using a 26-gauge needle. This procedure was done in conscious animals with no evidence of discomfort.**

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

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

# Research Applications 6

**Brain Administration**

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

Thisgaard et al.
**Highly E ffective Auger-Electron T herapy i n a n O rthotopic G lioblastoma X enograft M odel using Convection-Enhanced D eliverHighly E ffective Auger-Electron T herapy in a n O rthotopic Glioblastoma Xenograft Model using Convection-Enhanced Deliver**
Theranostics 2016, Vol. 6, Issue 12 2016; 6(12): 2278-2291. doi: 10.7150/thno.15898
http://www.thno.org/v06p2278.htm

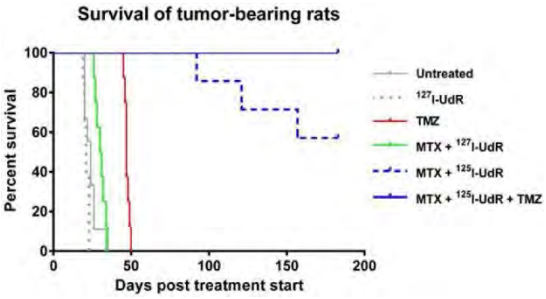



Figure 6. Kaplan-Meier plot showing that the survival benefit of neoadjuvant MTX + $^{125}$I-UdR as stand-alone Auger-therapy (group4) or with concomitant, systemic TMZ chemotherapy (group5) was highly significant compared with the non-radioactive, but chemically identical treatment MTX + $^{127}$I-UdR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

## Purpose of the study:

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

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

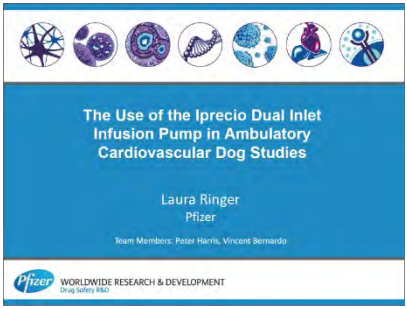
## Results/significance

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

## Research Need:

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

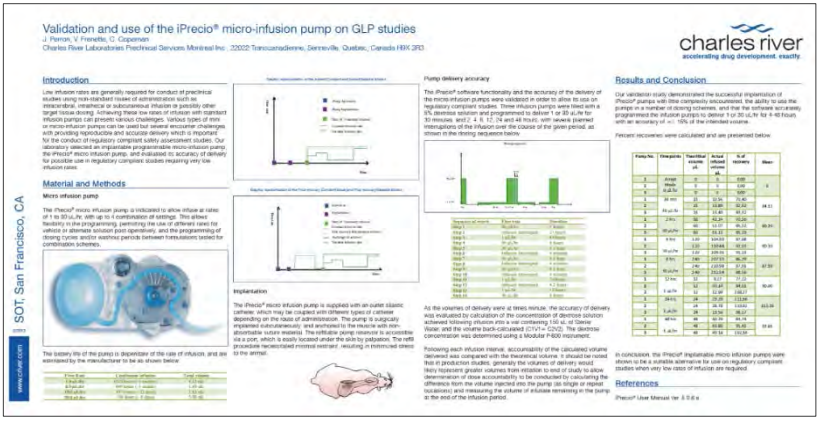
# GLP Studies with iPRECIO Pumps




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.
https://www.criver.com/getattachment/2740a3f0-d513-4930-9d8b-f6a974620b39/Validation-and-Use-of-the-iPrecio-Micro-Infusion-P.aspx

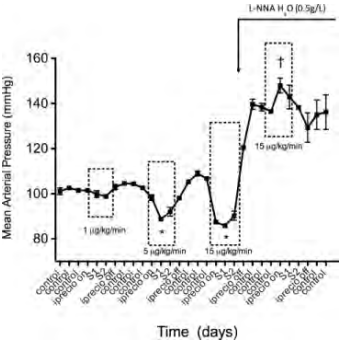



# Toxicology Studies with iPRECIO Pumps

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

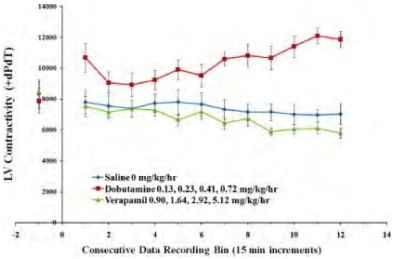
# Application Examples

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



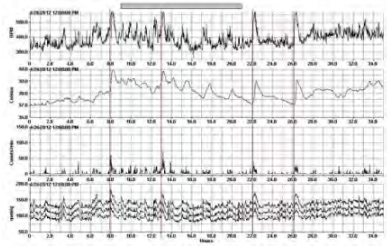

**Drug Delivery: Enabling Technology for Drug Discovery and Development.**
**iPRECIO® Micro Infusion Pump: Programmable, Refillable, and Implantable**
Tsung Tan, Stephanie W. Watts, and Robert Patrick Davis
Front Pharmacol. 2011; 2: 44. Published online 2011 July 29.
doi: 10.3389/fphar. 2011.00044

**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

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

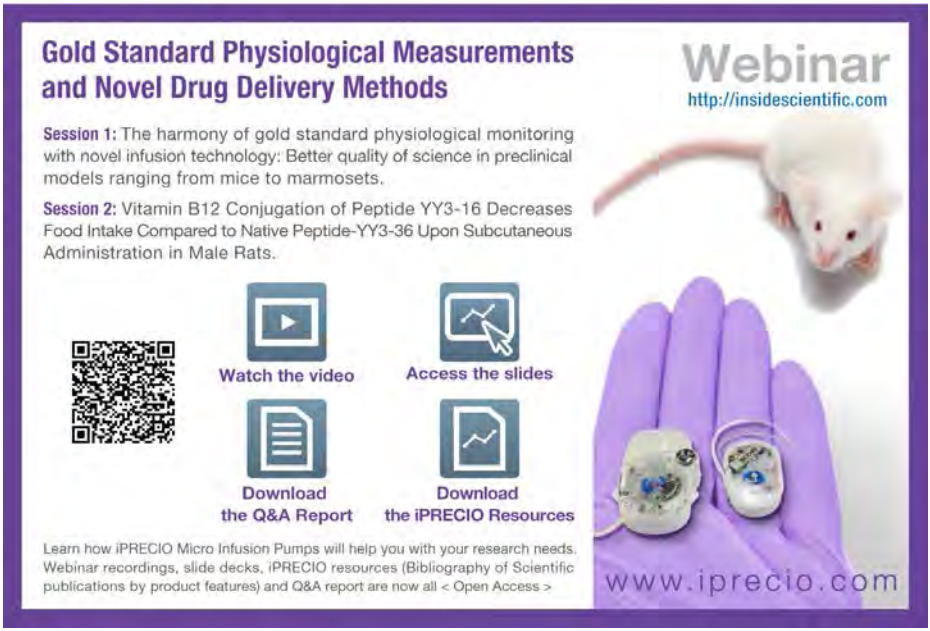


Zaretsky D.V., Zaretskaia M.V., Durant P.J., Rusyniak D.E.
**The use of microinfusion pump to perform intrahypothalamic injections in conscious rats.**
Neuroscience 2012, New Orleans, USA.,
October 13th - 17 2012

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

**Comparison of arterial pressure and plasma ANG II responses to three methods of subcutaneous ANG II administration**
Comparison of arterial pressure and plasma AngII responses to three methods of subcutaneous AngII administration
Kuroki M.T. . , Gregory D. Fink , John W. Osborn
American Journal of Physiology - Heart and Circulatory PhysiologyJul 2014, DOI: 10.1152/ajpheart.00922.2013
http://ajpheart.physiology.org/content/early/2014/06/30/ajpheart.00922.2013

# Webinar




**Dr Christian Schnell**

Want to see objective data which lead Dr Schnell to the following conclusions?

1. The best situation 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.

The open access on-demand webinar, resources, and Q&A are available 24/7.

**Dr Robert Doyle**

How are we going to know that if we do SC or Oral administration that we are not inducing a stress response which essentially negates the data we collect at the back end in terms of food intake and body weight as they pertain to our study?

Q: What were the best resources for learning how to program the iPRECIO mini pumps? Was it relatively simple?

Ans. [R. Doyle]:
Highly skilled technician used iPRECIO for the first time and did not have any difficulties and expect that similar skilled technicians to be fine. Medicinal chemists with only basic husbandry have been trained by technician (Monday–Friday week), to program and implant (surgery). Never lost a pump and never had a student screw-up.

**What drug delivery concerns did Dr. Robert Doyle have and how did he solve it?**
The open access on-demand webinar, slide deck, iPRECIO resources and Q&A are available 24/7. See also publication in Endocrinology.

1. We have to be particularly conscious of the fact that when looking at <Food Intake> and <Body Weight Reduction>, the handling of the animals is particularly confounding because inducing stress or inducing fight-or-flight response etc. is going to play havoc with our data collection.

2. And if we are dealing with subtle changes that can be the reason we lose out on seeing something we wouldn't otherwise and obviously that's something we were really really conscious of and concerned about when we began to do this project.

3. How are we going to know that if we do SC or Oral administration that we are not inducing a stress response which essentially negates the data we collect at the back end in terms of food intake and body weight as they pertain to our study?

Endocrinology Publication
**Vitamin $B_{12}$ Conjugation of Peptide-$YY_{3–36}$ Decreases Food Intake Compared to Native Peptide-$YY_{3–36}$ Upon Subcutaneous Administration in Male Rats**
Endocrinology February 6, 2015 doi: 10.1210/en.2014-1825
http://press.endocrine.org/doi/abs/10.1210/en.2014-1825

**SMP-200 iPRECIO Use**
- Recovery period after surgery of 7 days and 5 day baseline period (2µl/hr of saline)
- Treatments were delivered sc with five pulses per day; three 1 hour pulses of 10 $nmol.kg^{-1}.h^{-1}$ (20 $\mu l.h^{-1}$) with three hours between pulses and two 1 hour pulses of 5 $nmol.kg^{-1}.h^{-1}$ (10 $\mu l.h^{-1}$) with five hours between pulses.

# 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**

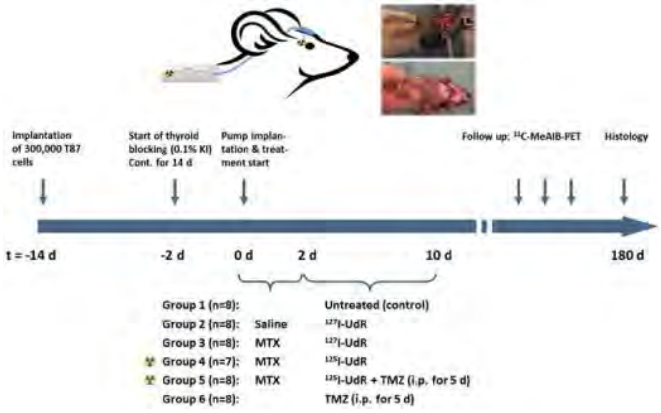



Figure 1 reproduced from Thisgaard et al. (CC BY-NC-ND 4.0)
Highly Effective Auger-Electron Therapy in an Orthotopic Glioblastoma Xenograft Model using Convection-Enhanced Delivery
Thisgaard et al. Theranostics 2016, Vol. 6, Issue 12 2016; 6(12): 2278-2291. doi: 10.7150/thno.15898

## Brain Infusion (Selected Publications)

Keisuke Shinohara, Toshimichi Hata

**Memory forgetting and NMDA receptor : Post-acquisition chronic micro infusion of NVP-AAM077 i nto d orsal h ippocampus s ubsequently i mpairs t he p erformance at reversal learning task in Morris water maze in rats**

The 39th Annual Meeting of the Japan Neuroscience Society, Oral Session Learning and Cognition: Hippocampus [O2-H-2-2] July 21, 2016.

http://www.jnss.org/abstract/neuro2016/meeting_planner/sessiondetail.php?st_id=2016000289&u=1469585803&yz=0

Gey et al.

**Continuous bilateral infusion of vigabatrin into the subthalamic nucleus : Effects on seizure threshold and GABA metabolism in two rat models**

Neurobiology of Disease Volume 91, July 2016, Pages 194–208 doi:10.1016/j.nbd.2016.03.012.

http://www.sciencedirect.com/science/article/pii/S0969996116300560

Yamato et al.

**Brain Interleukin-1β and the Intrinsic Receptor Antagonist Control Peripheral Toll-Like Receptor 3-Mediated Suppression of Spontaneous Activity in Rats**

Published: March 12, 2014 DOI: 10.1371/journal.pone.0090950 PLOS ONE Volume 9 Issue 3

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0090950

## Intrathecal Infusions (Selected Publications)

Matsubara et al.

**Secreted Ectodomain of Sialic Acid-Binding Ig-Like Lectin-9 and Monocyte Chemoattractant Protein-1 Promote Recovery after Rat Spinal Cord Injury by Altering Macrophage Polarity**

The Journal of Neuroscience, February 11, 2015 • 35(6):2452–2464

http://www.jneurosci.org/content/35/6/2452.short

Yamamoto et al.

**Analysis of the Neuroregenerative Activities of Mesenchymal Stem Cells in Functional Recovery after Rat Spinal Cord Injury**

Animal Models for Stem Cell Therapy

Methods in Molecular Biology Volume 1213, 2014, pp 321-328 Chapter 26 , 04 Aug 2014

http://link.springer.com/protocol/10.1007/978-1-4939-1453-1_26

## Pain Research

Imai et al.

**Inhibition of P2X4 receptor on spinal microglia attenuates mechanical allodynia in experimental autoimmune neuritis rats**

Pain Research, Vol. 26 2011, O-59

https://www.jstage.jst.go.jp/article/pain/27/1/27_4/_pdf

## Selected CNS Applications with iPRECIO Micro Infusion Pumps

**Addiction/ Drug abuse liability**

Examples

- 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

**Spinal Cord Injury Research**

**Tolerance**

**Pain Research**

**Program exposure profiles**

- to study impact on tolerance development (example: continuous v intermittent) Program exposure profiles to study impact of increasing or decreasing dose Verify reversibility (start and stop of drug delivery)

## Suggested Reading: EEG with iPRECIO Micro Infusion Pumps (Selected Publications)

Wood S.K., McFadden D.V., Grigoriadis D., Bhatnagar S. and Valentino R.J.

**Depressive and cardiovascular disease co-morbidity in a rat model of social stress: a putative role for corticotropin-releasing factor**

Psychopharmacology 2012 Feb 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/22322324

## Hot off the Press (Latest CNS Publication)

C. Laloux et al.

**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:**

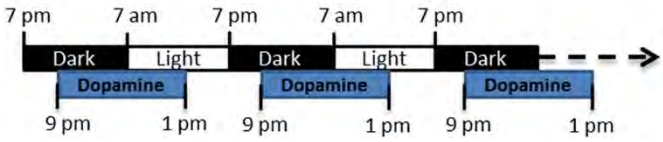



Image 1 & text reproduced without modification from C. Laloux et al. (CC BY-NC-ND 4.0)

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

Supplementary Image 1. Dopamine delivery from the pump trough the rat brain cannula begin each day from zeitgeber time - 10h (i.e. 9pm) to zeitgeber time 6 h (i.e. 1pm), over 16h during 30 days.

# iPRECIO Micro Infusion Pumps for Cancer Research

Solubility and 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

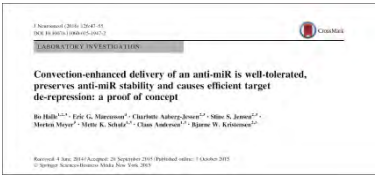
http://cancerres.aacrjournals.org/content/75/15_Supplement/5146.short

**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


LABORATORY INVESTIGATION

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

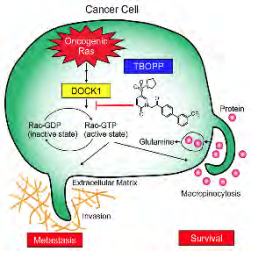
Tajiri et al. (Kyushu University, Japan)

**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

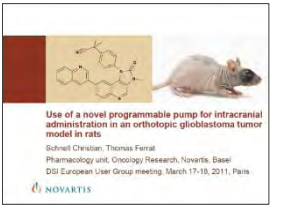





Christian R. Schnell (Oncology Research, Novartis, Switzerland)

**Use of iPRECIO implantable micro infusion pumps in rats**

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



# Selected Further Reading I

**> For More detailed Background iPRECIO and Drug Discovery, see**

**Drug Delivery: Enabling Technology for Drug Discovery and Development. iPRECIO® Micro Infusion Pump: Programmable, Refillable, and Implantable**
Front Pharmacol. 2011; 2: 44. Published online 2011 July 29. doi:10.3389/fphar.2011.00044
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149148/?tool=pmcentrez

**Discovering and Developing Molecules with Optimal Drug-Like Properties**
**Editors: Allen C Templeton, Stephen R. Byrn, Roy J Haskell, Thomas E. Prisinzano**
ISBN: 978-1-4939-1398-5 (Print) 978-1-4939-1399-2 (Online) 27 Sep 2014
http://link.springer.com/book/10.1007/978-1-4939-1399-2

**> For More Trends, see**

**Dosing-Time Makes the Poison: Circadian Regulation and Pharmacotherapy**
Dallmann, Robert et al.
Trends in Molecular Medicine , Volume 22 , Issue 5 , 430 – 445
http://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914(16)00056-3

**The right dose for every patient: a key step for precision medicine**
Richard W. Peck
Nature Reviews Drug Discovery 15, 145–146 (2016) doi:10.1038/nrd.2015.22
http://www.nature.com/nrd/journal/v15/n3/full/nrd.2015.22.html

**Animal-based studies will be essential for precision medicine**
K. C. Kent Lloyd, Peter N. Robinson and Calum A. MacRae
Science Translational Medicine 17 Aug 2016:
Vol. 8, Issue 352, pp. 352ed12, DOI: 10.1126/scitranslmed.aaf5474
http://stm.sciencemag.org/content/8/352/352ed12

**Can f ormulation and d rug d elivery r educe a ttrition during d rug d iscovery a nd development—review of feasibility, benefits and challenges**
S Basavaraj, Guru V. Betageri,
Acta Pharmaceutica Sinica B
Volume 4, Issue 1, February 2014, Pages 3–17
SI: Drug Delivery System and Pharmaceutical Technology
http://www.sciencedirect.com/science/article/pii/S2211383513001081

**Circadian Timing in Cancer Treatments**
Annual Review of Pharmacology and Toxicology Vol. 50: 377-421 (Volume publication date February 2010)
DOI: 10.1146/annurev.pharmtox.48.113006.094626
http://www.annualreviews.org/doi/abs/10.1146/annurev.pharmtox.48.113006.094626?journalCode=pharmtox

# Selected Further Reading II

(Miscellaneous Application Research Areas)

For comprehensive list, go to **www.iprecio.com** or contract Primetech Corporation.

## > Drug Discovery: iPRECIO Micro infusion pumps referenced

### Discovering and Developing Molecules with Optimal Drug-Like Properties

AAPS Advances in the Pharmaceutical Sciences Series, 2015
Editors: Templeton, A.C., Byrn, S.R., Haskell, R.J., Prisinzano, Th.E. (Eds.)
http://www.springer.com/jp/book/9781493913985?wt_mc=ThirdParty.SpringerLink.3.EPR653.About_eBook

### Enabling Discovery Through Leveraging and Miniaturizing Pharmaceutical Principles and Processes

Discovering and Developing Molecules with Optimal Drug-Like Properties
AAPS Advances in the Pharmaceutical Sciences Series Volume 15, 2015,
pp 95-140 Chapter 3, 27 Sep 2014,
http://link.springer.com/chapter/10.1007/978-1-4939-1399-2_3

### Discovery Formulations: Approaches and Practices in Early Preclinical Development

Discovering and Developing Molecules with Optimal Drug-Like Properties
AAPS Advances in the Pharmaceutical Sciences Series Volume 15, 2015,
pp 49-94 Chapter 2, 27 Sep 2014
http://link.springer.com/chapter/10.1007/978-1-4939-1399-2_2

### Optimising in vivo pharmacology studies-Practical PKPD considerations

Journal of Pharmacological and Toxicological Methods Volume 61, Issue 2,
March-April 2010, Pages 146-156, Troubleshooting methods in pharmacology and toxicology
http://www.sciencedirect.com/science/article/pii/S1056871910000183

## > Drug Discovery PK/PD

### Implementation of pharmacokinetic and pharmacodynamic strategies in early research phases of drug discovery and development at Novartis Institute of Biomedical Research

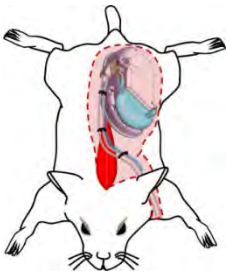
Front. Pharmacol., 28 July 2014 | http://dx.doi.org/10.3389/fphar.2014.00174
http://journal.frontiersin.org/article/10.3389/fphar.2014.00174/abstract

### Pharmacokinetics in Drug Discovery: An Exposure-Centred Approach to Optimising and Predicting Drug Efficacy and Safety.

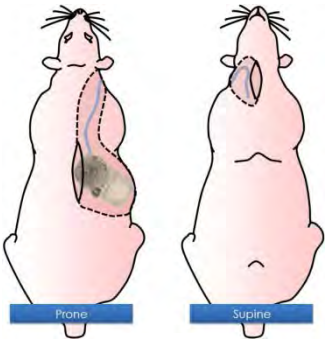
Handb Exp Pharmacol. 2016;232:235-60. doi: 10.1007/164_2015_26.
http://link.springer.com/chapter/10.1007%2F164_2015_26

# Example Pump implantation site and drug administration site

Intravenous Administration

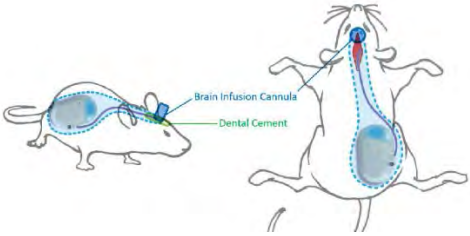


SMP-300

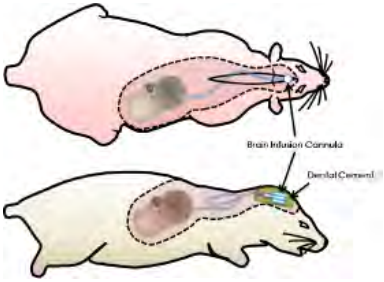



SMP-200

Intracerebral Administration




SMP-300




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.

# Surgical Videos

## Mouse Surgeries (SMP-300)

### SMP-300 with SC administration and general preparation video

https://drive.google.com/folderview?id=0B0pySJ1uXUqSVFBSVVAzTlZHaWc&usp=sharing

### SMP-300 with IP administration

https://drive.google.com/folderview?id=0B0pySJ1uXUqSd1BNdDVZeEFQUWM&usp=sharing

### SMP-300 with IV Jugular administration

https://drive.google.com/folderview?id=0B0pySJ1uXUqSbENyQ21nY2REcHM&usp=sharing

### SMP-300 with IV femoral administration

https://drive.google.com/folderview?id=0B0pySJ1uXUqSdlFtVFdJMFFncWM&usp=sharing

### SMP-300 with ICV administration

https://drive.google.com/folderview?id=0B0pySJ1uXUqSUGxHWkdLTXMwSEk&usp=sharing

### Refilling Video and Refiling FAQ

https://drive.google.com/folderview?id=0B0pySJ1uXUqSX203d1l4bGsxOG8&usp=sharing

## Rat Surgeries (SMP-200)

### Surgery Training Videos

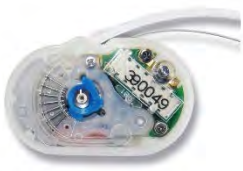
https://drive.google.com/folderview?id=0B0pySJ1uXUqSR2kzLVlMbWtRNUE&usp=sharing

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

| Model | SMP/IMS-300 | SMP/IMS-300 |
|---|---|---|
| Appearance of the pump |  |  |
| Type | Implantable SC | Implantable SC |
| Volume / Weight | 2.15cc / 3.3g | 7.20cc / 7.9g |
| Animal Species | Mouse or larger | Rats or larger |
| Reservoir Volume | 130 µL | 900 µL |
| Flow Rate (Setting Resolution) | 0.0 – 10.0 µL/hr (0.1µL/hr) | 0.0, 0.2, 0.5&1.0 – 30.0µL/hr (0.1µL/hr) |
| Flow Steps / Repeat | 15 / Yes | 10 / Yes |
| Battery Life | 0 & 0.1 ul/hour 46 days<br>1 µl/hour up to 33 days<br>10 µl/hour up to 9 days | 0, 0.2, 0.5, 1 µl/hour - 6 mths<br>2.5 µl/hour - 86 days<br>30 µl/hour - 8 days |
| Programmable | Wireless Preprogrammable | Preprogrammed prior to implantation |

Compatible solvents for SMP-300 and SMP-200
* Tested for both SMP-200 & SMP-300
* Tested in SMP-200 Pump Only
(same materials and manufacturing process) and expected to be compatible when compatible. Also, not compatible when not compatible.
---
Compatible Solvents
---
Acids, with pH 2 or weaker *
Bases, with pH less than 13 *
Buffered Phosphate Saline (PBS) *
Culture Media (1% benzyl alcohol) *
Cyclodextrin *
Dextrose, up to 5% in water or saline *
N,N-Dimethyl formamide (DMF), up to 25% in water *
DMSO 50% and water or saline 50% *
DMSO, up to 50% in ethanol (≤15%) and water *
DMSO 5% and PEG400 95% *
50% DMSO + 50% Propylene Glycol *
DMSO 50% and water 50% *
DMSO 50% + 15% ethanol and 35% water *
Dulbecco's Modified Eagle Medium (D-MEM) (1X), liquid *
Ethanol, up to 50% in water *
Glycerin, up to 75% in water *
Glycerol 100% *
1-Methyl-2-Pyrrolidone, up to 12.5% in water *
Propylene Glycol *
Ringer's solution (without lactate) *
Saline, 0.9% (or other aqueous salt solution) *
Triacetin, up to 5% in water *
Tween 80, up to 2% in water *
Water, distilled *
PEG200 100% *
Solutol® 15% in water *
---
Viscosity up to 20 cp is ok.
(Higher viscosity not tested due to the use of 27G needles.
Difficulty to aspirate solution with 27G needle)
---
Short term use only (1 - 2month)
---
PEG300 100% * (< 45 days)
PEG400 100% *
Cremophor EL 25% in water * (< 30 days)
PEG400/Propylene Glycol/Water 30：50：20 * (< 30 days)

Rev08 June 2017

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