Tabular highlights gives a high level view of how iPRECIO pumps were used/programmed in selected scientific publications in Applications Examples eBook. For more detailed view, refer eBook and publications . In e-book for example, Research Application 1 (RA1) on page 5 & 6 of eBook is on row 1 of Tabular highlights – Chavan et al. The protocol is once a day infusion. RA2 on pages 7 & 8 (row 2 Kroon et al) has a 3 day stop prior to start of infusion of Nicotinic acid with the animal in the metabolic cage all of the time of the infusion protocol.

Research Application (RA), Author, doi:	Refillability of Pump		How pump programmed?			Adminstration Site	Key words	Duration
	KVO/RCV	Vehicle and Drug(s)	Continuous	Intermittent or bolus	Circadian / Timed release			
RA 1 Chavan et al. doi:10.1038/ncomms10580 pgs 5-6 of eBook	1 week recovery	Pumps programmed to infuse saline (2ul/hr) or ßOHB (2ul/hr) or sodium pyruvate (5ul/hr) or coconut oil (5ul/hr) prior to meal time (6h, ZT22-ZT) in Restricted Food (RF)	No	Yes	Yes	SC	Biological sciences-Neuroscience-Biochemistry Mice + SMP-300 iPRECIO Pump	< 3 weeks
RA 2 Kroon et al. doi: 10.1194/jlr.M058149 pgs 7-8 of eBook	Pump programmed to stop for 3 days	Nicotinic Acid (NiAc) or saline 5 days of continuous or intermittent (12 hr ON/OFF cycles, infusion on 13:00h)	Yes	Yes	Yes	SC	Adipose tissue-diabetes-drug therapy-Lipoysis and fatty acid metabolism-GPR109A-Niacin-Tachyphylaxis Zucker rat + SMP-200 Pump	5 or 11 days infusion + 2 days recovery
RA 3 Suehiro et al. doi:10.1038/srep04972 pgs 9-10 of eBook	No	PKA and ATP - solution change every 2 days 1ul/hour	Yes	No	No	intrathecal	Neural-stem cells-spinal cord injury rat + SMP-200 Pump	14 days
RA 4 Mitchell et al. Developments in LifeSciences Vol. 14 No. 4 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-EE8FA14CD9F1%7d pgs 11-12 of eBook	1ul/hr saline for 1 week for full recovery	Test articles infusing at 30ul/hr for 72 hours after 1ul/hr saline recovery after catherization and pump implantation	Yes	No	No	intrathecal	Regulatory request, CNS end points (modified Irwin assessment) rat + SMP-200 Pump	10 days
RA 5 Asemu et al. DOI: 10.1152/ajpheart.00674.2012 pg 13 of eBook	No	Aldosterone (15% ethanol 50% DMSO and 35% water) was continuous infused	Yes	No	No	IV jugular	Cardiac, diastolic dysfunction, heart failure, metabolism dog + SMP-200 Pump	14 weeks
RA 6 Thisgaard et al. DOI: 10.7150/thno.15898 pg 14 of eBook	No	isotone saline, 0.1 mM MTX, then 0.3µg/ml ^{125}I-UdR, ^{127}I-UdR was continuously infused	Yes	No	No	Brain infusion	Glioblastoma, Auger-electron therapy, convection delivery, [^{125}I}5-Iodo-2'-deoxyuridine, temozolomide, SMP-200 Pump	10 days
Author, doi:								
GLP Studies with iPRECIO Pumps (page 15 eBook)								
Patten et al pg 15 of eBook	1ul/hr artificial CSF	Treament period 30ul/hour for 72 hours	No	Yes	Yes	intrathecal	CNS (modified Irwin assessment) rat + SMP-200 pump	3 days for TA
Perron et al pg 15 of eBook	No	Flow-rate and dosing validation studies on the bench	No	Yes	Yes	in-vitro	GLP validation	< 7 days
Ringer et al pg 15 of eBook	Saline when not infusing test article	2 hour baseline, 2 hour infusion (Milrinone or vehicle)	No	Yes	Yes	right jugular vein	GLP validation, jacktet, ambulatory, cardiovascular Dog + iPRECIO Dual	24 hours
Author, doi:								
Toxicology with iPRECIO pumps (page 15 eBook)								
Tsuboi et al. http://doi.org/10.2131/fts.3.1 pg 15 of eBook	No but full study saline infusion	Saline infusion for 4 weeks and 13 weeks 2 or 2.5ul/hour	Yes	No	No	IV jugular	Infusion pump, implantation, rat, iPRECIO, Physiological condition SMP-200 pump	4 or 13 weeks
Application (PA), Author, doi:								
Application Examples pg 16 of eBook								
AP1 Tan et al. 5-HT doi: 10.3389/fphar.2011.00044 pg 16 of eBook	3 days pump "OFF" (0.2ul/hour) , for control cardiovascular parameters	5-HT dose response with control period	No	Yes	Yes	sc	drug delivery, minipump, osmotic pumps, implantable pump, dose response, quantitative pharmacol-ogy, preclinical, telemetry rat + SMP-200 pump	30 days
AP2 Tan et al. dobutamine doi: 10.3389/fphar.2011.00044 pg 16 of eBook	11 day recovery period	Saline, dobutamine and verapamil infusions	No	Yes	Yes	IV	drug delivery, minipump, osmotic pumps, implantable pump, dose response, quantitative pharmacol-ogy, preclinical, telemetry rat + SMP-200 pump	30 days

Research Application (RA), Author, doi:	Refillability of Pump		How pump programmed?			Adminstration Site	Key words	Duration
	KVO/RCV	Vehicle and Drug(s)	Continuous	Intermittent or bolus	Circadian / Timed release			
AP3 Zaretsky et al. 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 pg 16 of eBook	5 day recovery but no flow	BMI (0.1 mM) 100 nl injections	No	Yes	Yes	intra-hypothalamic	hypothalamas, cardiovasular, micro injections rat + SMP-200 pump	several days
AP4 Kuroki et al. DOI: 10.1152/ajpheart.00922.2013 pg 16 of eBook	7 to 10 days recovery then 4 days control period	5ul/hour continous infusion of Ang II. Comparison made with Alzet Pump and Havard Sringe pump	Yes	no	No	SC administration	salt-sensitive hypertension; angiotensin II-salt hypertension; Alzet salt-sensitive hypertension; minipump; iPrecio pump; plasma angiotensin II	2 weeks Ang II infusion
AP5 Gey et al. doi:10.1016/j.nbd.2016.03.012 not in eBook	no RCV	0.2 ul/hr continuos infusion. Stability of vigabatrin was tested and confirmed for 5 weeks	yes	no	no	Bilateral infusion into STN or anterior SNr	minipump; iPrecio pump; plasma angiotensin II Rats, SMP-200	3 or 4 week
Webinar (WE), Author, www or doi								
Webinar: **Compound Delivery, PK-PD & Validation Studies in Oncology Studies**. Schnell et al. http://www.insidescientific.com/webinars/item/384-gold-standard-physiological-measurements-and-novel-drug-delivery-methods-iprecio *pg 17-18 of eBook*	RCV or KVO not discussed	2 pumps (SMP-200 & SMP-310R) 3 tool compounds, 24 doses, 7 infusion rates (2.2ul/hr to 20 ul/hr)	Yes	No	No	iv, external jugular vein	PK/PD, oncology, tool compounds, validation, programmable pump	12-13 days
WE 1 Schnell http://www.insidescientific.com/webinars/item/384-gold-standard-physiological-measurements-and-novel-drug-delivery-methods-iprecio pg 17-18 of eBook	Saline infusion for tumor size to grow to a certain size (12th day)	On day 21 (tumor reached certain size), infusion of Compound A for 22 days. Behaviour and weight gain not impaired versus control without subcutaneous pump	Yes	No	No	Intra-cranial infusion	Cancer,orthotopic,glioblastoma, bioluminecscence Nude rats, SMP-200	22 days
WE 2 Doyle http://www.insidescientific.com/webinars/item/384-gold-standard-physiological-measurements-and-novel-drug-delivery-methods-iprecio pg 17-18 of eBook	7 days recovery Saline 5 days baseline Saline 5 day TA or 10 day TA	**Vitamin B12 Conjugation of Peptide-YY3–36 or Native Peptide-YY3–36 or saline** 5 pulses per day; three 1 hour pulses of 10 nmol.kg-1.h-1 (20 µl.h-1) with three hours between pulses and two 1 hour pulses of 5 nmol.kg-1.h-1 (10 µl.h-1) with five hours between pulses	No	Yes	Yes	subcutaneous	endocrinology vitamin B12, BBB, reduction of food intake, peptides rats, SMP-200 pumps	5 or 10 days
Henry et al. DOI: http://dx.doi.org/10.1210/en.2014-1825 (WE 2) pg 18 of eBook	7 days recovery Saline 5 days baseline Saline 5 day TA or 10 day TA	**Vitamin B12 Conjugation of Peptide-YY3–36 or Native Peptide-YY3–36 or saline** 5 pulses per day; three 1 hour pulses of 10 nmol.kg-1.h-1 (20 µl.h-1) with three hours between pulses and two 1 hour pulses of 5 nmol.kg-1.h-1 (10 µl.h-1) with five hours between pulses	No	Yes	Yes	subcutaneous	endocrinology vitamin B12, BBB, reduction of food intake, peptides rats, SMP-200 pumps	5 or 10 days
Additional Highlights, doi								

Research Application (RA), Author, doi:	Refillability of Pump		How pump programmed?			Adminstration Site	Key words	Duration
	KVO/RCV	Vehicle and Drug(s)	Continuous	Intermittent or bolus	Circadian / Timed release			
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 Page 22 of eBook.	KVO function not used	Development of the pregnant rat model for labor induction and augmentation with Oxt. The system consists of a subcutaneously placed iPRECIO infrared-controlled microinfusion pump (SMP-200, Primetech Corporation) connected to the right internal jugular vein in an embryonic day (E)18 Sprague Dawley dam (Charles River Laboratories) (Fig. 2). Briefly, the dam was anesthetized with 2% isoflurane followed by subcutaneous implantation of the iPRECIO pump approximately 2–3 cm below the nape of the neck and creation of a tunnel to deliver the pump tubing next to the internal jugular vein, into which it was secured in place with ligatures. The reservoir of the iPRECIO pump was primed with sterile normal saline prior to implantation and was pre-programmed to deliver an infusion rate of 10 µl/h for 72 h to keep the tubing patent until E21. Two hours before completion of the saline infusion at 72 h, the reservoir was accessed subcutaneously under brief isoflurane anesthesia to aspirate the saline and was refilled with 900 µl of Oxt (Selleck Chemicals, 50 µg/mL in normal saline). This was followed by the pre-programmed infusion rate of 5 µl/h for 4 h, 10 µl/h for 4 h, 20 µl/h for 4 h, and 30 µl/h for 12 h (iPRECIO Management System) (Supplementary Fig. S2).	Yes, dose escalation. 4 doses or flow-rates	No	No	IV right jugular	Subjects Preclinical research Translational research	
Dey et al. DOI https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.118.312708 Page 25 of eBook.	No	Daily bolus of Isoproterenol (ISO) was administered via implantation of a programmable iPRECIO® Pump in the peritoneal cavity. The iPRECIO pump enables reliable, timed delivery of pharmacological agents. The pump was programmed for 1 hour delivery of Isoproterenol at 30µl/hr, total dose of 2mg/kg/day, once a day at the same time (1 PM).	no	Yes	Yes	IP	ventricular fibrillation, phosphorylation, proteomics, heart failure, reactive oxygen species, mitochondria 300g hartley guinea pig, SMP-200	3 to 5 weeks
Steplewski et al https://onlinelibrary.wiley.com/doi/abs/10.1002/jor.23369 New: Not referenced in E-Book	No	The delivery of the ACA and P-ACA started immediately after surgery and continued for 8 weeks at 1ul/h.	Yes	No	No	injured knee joint	joint contracture, posterior capsule collagen, collagen fibrils, arthrofibrosis, antibody New Zealand White Rabbits, 8-12mths, SMP-200	8 weeks

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Jul-22

For more details on applications, see **bibliography section** (here) and **iPRECIO® Application and Technology Report** (here)

Continuous delivery of lenalidomide and other immunomodulatory agents **Mouse Update 1 (MU1) Borovinskaya et al**. US Patent Application US 2020/0330445A1 See Example 1 https://patents.google.com/patent/US20200330445A1/en?q=iprecio&q or https://lnkd.in/gerJdDA *pg 27 of eBook*	24 hour stop after surgery before drug delivery then 4ulhr. Replace pump after 2 weeks, 24 stop after surgery before continuing	24 hour stop after surgery before drug delivery then 4ulhr. Replace pump after 2 weeks, 24 stop after surgery before continuing	Yes	No	No	SC	SCID mice, average weight of mice - 20g continous infusion	28 days

Research Application (RA), Author, doi:	Refillability of Pump		How pump programmed?			Adminstration Site	Key words	Duration
	KVO/RCV	Vehicle and Drug(s)	Continuous	Intermittent or bolus	Circadian / Timed release			
An adipokine feedback regulating diurnal food intake rhythms in mice **Mouse Update 2 (MU2) Tsang et al.** Tsang et al. eLife 2020;9:e55388. DOI: https://doi.org/10.7554/eLife.55388 Cite as: eLife 2020;9:e55388 DOI: 10.7554/eLife.55388 https://elifesciences.org/articles/55388 *pg 28 of eBook*	2 weeks recovery 0.5ul/hr	After 2 weeks of recovery (MT experiment; Figure 4) or after 6 weeks of HFD (WT HFD experiment; Figure 6), infusion of AdipoRon (1 mg/ml) or vehicle (DMSO/aCSF/PEG-400) was started, either cyclically with infusions starting at ZT13 for 10 hr followed by 14 hr of inactivity or constantly with a maximal flow of 0.5 ul/hr (for treatment regimens see Figures 4A and 8A). Pumps were re-freshed every 7-8 days and 3-4 days after re-freshing, feeding data taken at the appropriate time - ZT4-6.	Yes	Yes	Yes	ICV	8-week-old Adipoq-/- or WT mice. Circadium rhythms, Adipoq-deficient mice or wild-type mice - 8 weeks of age	3 weeks of rhymic or constant icv
A combination of two human monoclonal antibodies cures symptomatic rabies **MU3 Dias de Melo et al.** https://doi.org/10.15252/emmm.202012628 pg 28 of eBook	(i) a flow rate of 0.1 ll/h, to keep the pump delivering PBS from the day of surgery on; (ii) a flow rate of 1.0 ul/h, 2 days before the treatment, to allow flow stability and dead volume elimination from the tubing (27.4 ul)	The pumps were activated the day before the surgery using three infusion programs: (i) a flow rate of 0.1 ll/h, to keep the pump delivering PBS from the day of surgery on; (ii) a flow rate of 1.0 ll/h, 2 days before the treatment, to allow flow stability and dead volume elimination from the tubing (27.4 ll); and **(iii) a flow rate of 1.0 ll/h during 20 days to deliver the treatment.**	yes	No	Yes, precise timing with respect to clinical signs.	icv	Eight-week-old female SPF Balb/cJRj mice	20 days delivery of antibody cocktail following saline infusion for 2-3 days.
Sympathetic Overactivity in CKD Disrupts Buffering of Neurotransmission by Endothelium-Derived Hyperpolarizing Factor and Enhances Vasoconstriction **MU4 Cao et al.** DOI: https://doi.org/10.1681/ASN.2020030234 https://jasn.asnjournals.org/content/31/10/2312 pg 28 of eBook	N/A	To study the effects of inhibiting central sympathetic outflow, groups of 5/6Nx mice received continuous intracerebroventricular (i.c.v.) infusions of clonidine (5.76 mg/kg per day; Sigma, St. Louis, MO)5 or artificial cerebral spinal fluid (Sigma) from the first day after operation for 4 weeks, using Micro Infusion Pumps (iPrecio SMP/IMS-310R model, Durect Corporation, Cupertino, CA). Micro Infusion Pumps were implanted in mice under anesthesia 7 days before the 5/6Nx operation, and were programmed wirelessly using proprietary iPrecio pump software (Durect Corporation). The accuracy of the i.c.v. infusion was confirmed by the tracer Evans blue.	Yes	No	No	icv	Male CD1 mice, 6 week old Male CD-1 mice (6 weeks old) weighing 20–24 g were obtained from the Institutional Animal Experiment Center.	4 weeks
Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through α7nAChR+ splenocytes **MU5 Inoue et al.** https://doi.org/10.1172/JCI83658 https://www.jci.org/articles/view/83658 pg 28 of eBook	During the recovery period, normal saline was continuously infused at the rate of 1 µl/h for 4 days.	The catheter part of the microinfusion pump was inserted into the left external jugular vein via a midcervical incision. The main body of the microinfusion pump was implanted s.c. in the lumbar region. One day before LPS infusion, mice were anesthetized (ketamine [120mg/kg] and xylazine [12 mg/kg]) and the left cervical vagus nerve (uncut) was electrically stimulated (50 µA, 5 Hz, 1 ms) for 10 minutes as described above. At the infusion start time, normal saline in the microinfusion pump was changed to the LPS solution (10 µg/ml) under isoflurane anesthesia. LPS was infused at the rate of 10 µl/h for 3 hours. At the end of infusion, mice were anesthetized (ketamine [120 mg/kg] and xylazine [12 mg/kg]) and blood was collected from the periorbital sinus. Plasma TNF-α was measured with a commercially available ELISA kit (Affymetrix).	Yes	No	No	IV jugular	C57BL/6J male mice Mice. Male mice (8–12 weeks of age, 20–25 g) were used for all experiments. WT C57BL/6 mice were purchased from the National Cancer Institute, Chrna7–/– (referred to as α7KO) mice (B6.129S7-Chrna7tm1Bay/J) were obtained from Jackson Laboratories, and WT (Chrna7+/+) progeny were used as controls in experiments depicted in Figures 8 and 10.	10ul/hr for 3 hours LPS

Research Application (RA), Author, doi:	Refillability of Pump		How pump programmed?			Adminstration Site	Key words	Duration
	KVO/RCV	Vehicle and Drug(s)	Continuous	Intermittent or bolus	Circadian / Timed release			
Pulsative gnrh administration for treating cognitive disorders **MU6 PREVOT et al.** International Publication Number WO 2020/221821 A1; https://patents.google.com/patent/WO2020221821A1/en?q=PULSATIVE+GNRH+ADMINISTRATION+FOR+TREATING+COGNITIVE+DISORDERS&oq=PULSATIVE+GNRH+ADMINISTRATION+FOR+TREATING+COGNITIVE+DISORDERS pg 28 of eBook	N/A	Pulsatile GnRH infusion reverses both olfactory- and cognitive-related impairments in Ts65Dn mice. (A) Schematic diagram illustrating the pharmacological therapy performed in adult Ts65Dn mice with LUTRELEF®, a GnRH peptide of clinic use. Mice were implanted with osmotic pump, to receive a continuous infusion of vehicle or LUTRELEF® (0.25 pgr/ 3h); or with a programmable mini-pump (iPRECIO), to receive a pulsatile LUTRELEF® infusion (every 3 hours; a peak of 0.25 pg with peak duration of lOmin). (B-F) Representative graphs for LH pulsatility assessment after 15 days of vehicle or LUTRELEF® subcutaneous administration. LUTRELEF® pulsatile infusion in Ts65Dn males significantly increased LH pulse frequency and LH pulse amplitude (G) compared to LUTRELEF® continuous infusion which prevented both LH pulse frequency and LH pulse amplitude both in WT and Ts65Dn mice(G). LUTRELEF® pulsatile infusion rescued the capacity to discriminate between different odors (H) and cognitive deficits (I) in Ts65Dn mice. *p < 0.05; ** p < 0.01; *** p < 0.001.	No	Yes	Yes	ICV	mouse model of Down syndrome (DS - Ts65Dn mice)	2 weeks
Discovery, Preclinical Characterization, and Early Clinical Activity of JDQ443, a Structurally Novel, Potent, and Selective Covalent Oral Inhibitor of KRASG12CMU6 **MU6 Andreas Weiss et al.** https://aacrjournals.org/cancerdiscovery/article/12/6/1500/699171/Discovery-Preclinical-Characterization-and-Early 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. [Open Access]	Unknown (not described in detail)	To assess the effect of continuous dosing on tumor growth, LU99 tumor–bearing nude mice were implanted subcutaneously with a programmable microinfusion pump (iPRECIO, SMP310R, Primetech Corporation) as previously described (56). For this purpose, the catheter connected to the microinfusion pump was inserted into the left external jugular vein via midcervical incision, and the body of the microinfusion pump was implanted subcutaneously on the flank of the mice opposite to the xenograft tumor. For infusion, JDQ443 was dissolved in 30% PEG and 10% Kolliphor at a concentration of 3 and 10 mg/mL. The infusion rate of 4 µL/h was programmed with iPRECIO Management Software v1.0.4.0. Pumps were refilled with vehicle or JDQ443 daily. At days 2 to 3, 9 to 10, and 12 to 13, the drug released was quantified in blood samples collected at the tail vein by LC-MS/MS. “excerpt without modification according to Attribution-Non Commercial-No Derivatives 4.0 International (CC BY-NC-ND4.0) https://creativecommons.org/licenses/by-nc-nd/4.0/	Yes	No	No	IV external jugular vein	Mice were kept under optimal hygiene conditions in individually ventilated cages under 12-hour dark/12-hour light conditions and had access to sterilized food and water ad libitum. Subcutaneous tumors were induced by injecting cells in HBSS containing 50% BD matrigel in the flank of female athymic Crl:NU(NCr)-Foxn1nu-homozygous nude mice (Charles River; MIA PaCa-2, NCI-H2122, NCI-H441 5 × 106; LU99 2 × 106) or female CB17.Cg-PrkdcscidLystbg-J mice (Charles River; KYSE410 10 × 106). Subcutaneous NCI-H2030 and HCC44 tumors were induced by transplantation of tumor fragments in the flank of female C.B-Igh-1b/GbmsTac-Prkdcscid-Lystbg N7 mice (Taconic).	13 days at least