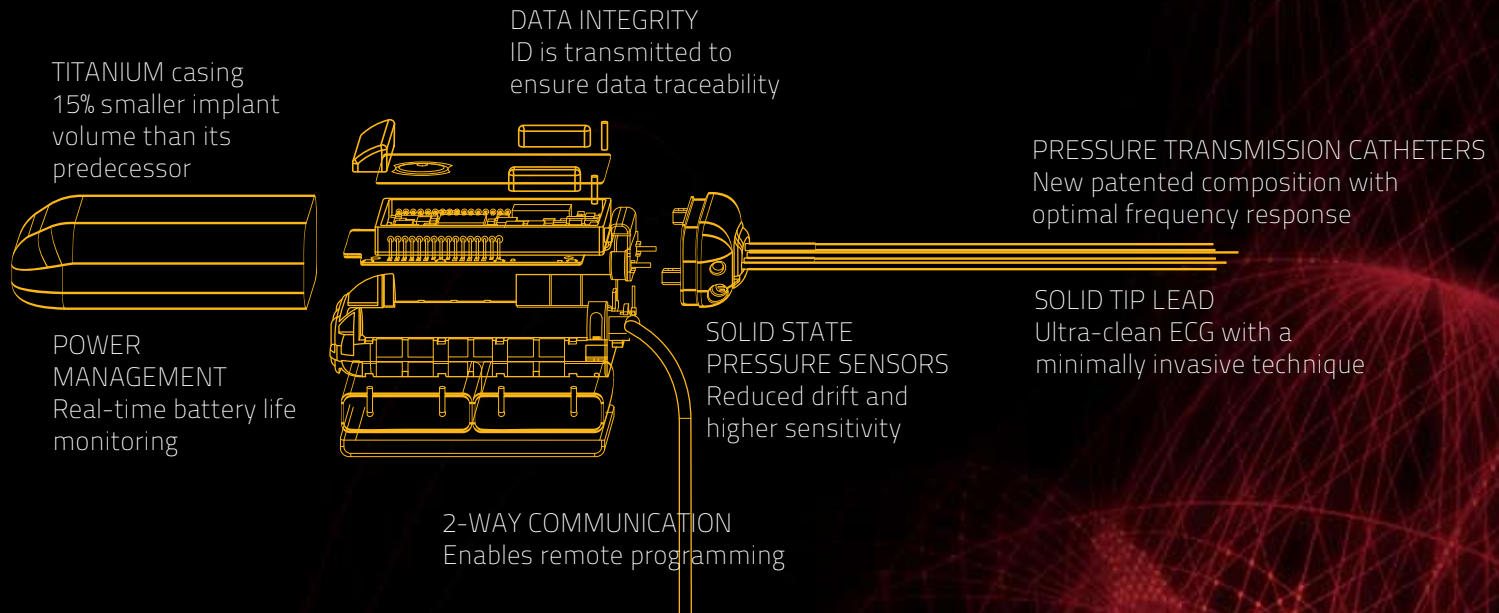


Introducing DSI TruSense® and TruData.®

DSI TruSense® Telemetry

The latest in digital sensing technology for precisely collecting physiologic information



TITANIUM casing
15% smaller implant volume than its predecessor

DATA INTEGRITY
ID is transmitted to ensure data traceability

PRESSURE TRANSMISSION CATHETERS
New patented composition with optimal frequency response

POWER MANAGEMENT
Real-time battery life monitoring

SOLID STATE PRESSURE SENSORS
Reduced drift and higher sensitivity

SOLID TIP LEAD
Ultra-clean ECG with a minimally invasive technique

2-WAY COMMUNICATION
Enables remote programming

GROUP HOUSING
Enhance animal welfare and efficiently use lab space



DSI TruData® Software

Signal to summary: acquire, synchronize, analyze, and report from many physiologic sources

EASE OF USE
Automated configuration of calibrations, remotely control sampling



See DSI TruSense® and TruData® while at the Safety Pharmacology Society Meeting!

POWERFUL
Maximizes the latest computer technology leveraging proven and robust analysis modules

EFFICIENT & FLEXIBLE
- Swift and easy system configuration
- Flexible sampling capabilities

Anthrax Toxins Induce Shock in Rats by Depressed Cardiac Ventricular Function [Watson et al, 2007]

Anthrax (*Bacillus anthracis*) infection carries a grave prognosis: the organism may cause disease through occupational exposure and poses a real risk through bioterrorism. Although aggressive therapy with antibiotics early during infection may be effective against the bacterium, no specific therapies exist for managing the consequences of toxin production. Profound hypertension and shock which are resistant to standard treatments characterise anthrax infection. Watson and co-authors describe the use of telemetry in combination with echocardiography to investigate the haemodynamic effects of the different purified *B. anthracis* toxins (protective antigen – PA, lethal factor – LF and edema factor – EF). PA combines with LF to form anthrax lethal toxin (LeTx) and with EF to form anthrax edema toxin (EdTx). Studies were performed in 180-230g male Sprague-Dawley rats. Initial experiments identified doses of toxins that resulted in 58% survival (LeTx) and

42% survival (EdTx).

Having established a model with delayed lethality, rats for haemodynamic studies were surgically implanted with miniature telemetry probes (DSI) with the blood pressure catheter inserted via the right carotid artery into the aortic lumen. Following a 7 day postsurgical recovery period, baseline blood pressure recordings were made over 3 days prior to intravenous injection of toxin (LeTx or EdTx) or vehicle. Post dosing recordings were made for periods of up to 72 hours. Echocardiography was performed in an additional cohorts of rats at 12-24 hours pre dose (baseline) and then at 1, 2, 3 and 24 hours after toxin injection. Scanning was carried out under general anaesthesia using ketamine and xylazine injection. Toxin concentrations from experimental groups were assayed using an ELISA method.

LeTx injection was followed by a rapid (within 1 hour) fall in heart rate and

blood pressure in telemetric data. Echocardiography revealed increases in velocity of propagation (V_p), left ventricular systolic area (LVSA) and left ventricular diastolic area (LVDA). Taken together, these data are interpreted as a direct effect of LeTx on the myocardium. EdTx injection was followed by a more delayed (18-48 hours) fall in blood pressure (systolic, diastolic and mean) with widened pulse pressure. Heart rate was increased but there were no other significant effects upon echocardiographic findings which was interpreted as a response to reduced preload. Results from this study show how cardiovascular data from telemetry of awake animals combined with haemodynamic data from echocardiography may shed light upon the sites and mechanisms of action of anthrax toxins.

Watson, L; Kuo, S; Katki, K; Dang, T; Park, S; Dostal, D; Tang, W; Leppla, S; Frankel, A. *PLoS ONE*. May 2007.

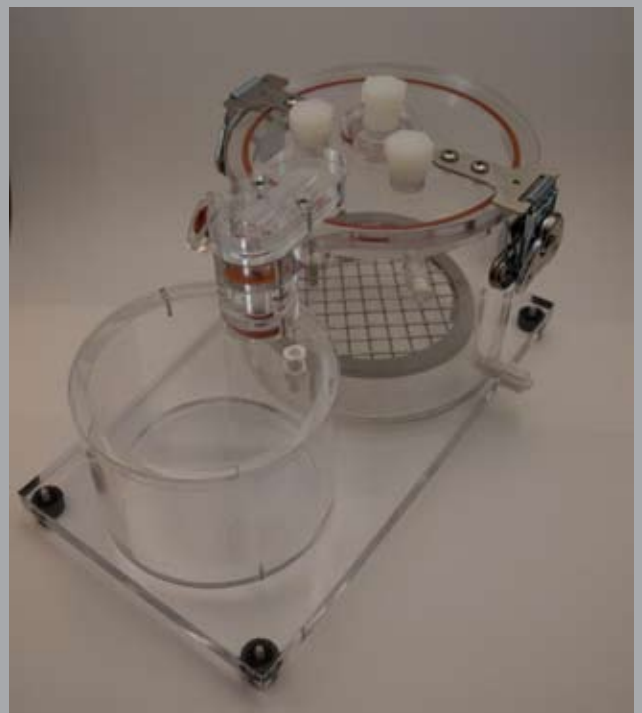
New Product Announcement: Mouse Whole Body Plethysmograph Chamber

DSI's plethysmography chambers are ideal for respiratory rate and tidal volume assessments.

The DSI Mouse Unrestrained Whole Body Plethysmograph, similar to the Rat Unrestrained Whole Body Plethysmograph Chamber, enables researchers to monitor physiologic endpoints from unrestrained mice such as:

- Breaths-per-Minute (BPM)
- Tidal Volume, Minute Volume
- Inspiratory time
- Expiratory time
- Pause and PenH

Don't forget that DSI is the only company that offers PhysioSync to digitally synchronize your hardwired signals with telemetric signals!



Cardiovascular Function in Nonclinical Drug Safety Assessment: Current Issues and Opportunities [Sarazan et al 2010]

The last 20 years have seen considerable advance in technologies and guidelines for nonclinical safety assessment of compounds undergoing development as new medicines. In spite of this, significant risks occasionally emerge late in clinical trials. To address such issues, the International Life Sciences Institute – Health and Environmental Sciences Institute (ILSI-HESI) hosted a meeting of stakeholders from industry, government and academia in Washington DC (USA). A working group convened during this meeting addressed “functional cardiovascular safety in drug development” and this publication summarizes its ongoing discussions and conclusions to date. While conscious animal telemetry remains an important contributor to safety pharmacology, the working party looks also at the relevance of anaesthetised and *in vitro* assays. Factors which impact the sensitivity and specificity of assays in safety pharmacology are evaluated. The differences in behavior of biological molecules from conventional small organic molecules need to be considered in design of safety pharmacology studies.

Considerable emphasis has been placed upon electrophysiology – particularly QT prolongation. Less emphasis has been placed upon hemodynamic parameters and effects of chronic (repeated) administration in safety pharmacology guidelines. Study design (Latin square, parallel and escalating dose) have impact on the sensitivity: behavior of the test compound (metabolism or permanent effects) will also impact the choice of study design. Small changes in systemic arterial blood pressure in human populations are associated with increased cardiovascular risk which makes study of blood pressure and heart rate highly desirable. Compound-induced hypertension may be acute or chronic in onset (depending upon the class of compound and mechanism of action). There is, however, no experimental

evidence from compounds known to induce small degrees of hypertension in human populations from conventional safety pharmacology methods. This is viewed as a significant research opportunity.

Generation of safety pharmacology data during toxicology studies is attractive since there is repeated dosing which could reveal effects not seen with acute dosing but the much higher dose levels employed have potential for mechanistic influences and data is obtained under very different conditions. Toxicology studies generally have different experimental designs from safety pharmacology experiments. Technical advances in electrocardiographic (ECG) recording for restrained animals or ambulatory telemetry with jacket systems, together with progress in signal handling and analysis, provide improved ECG data during toxicology studies although the impact of miniature implantable telemetry devices on background pathology remains to be fully evaluated.

Traditionally, more detailed hemodynamic assays such as myocardial contractile function (left ventricular pressure) have been regarded as additional studies for particular circumstances. The role and value of such studies is discussed with relevance to safety pharmacology. The potential for increased use of contractility studies is raised – particularly as a number of drugs known to induce heart failure are used in non-cardiac indications. Since a permanently implanted pressure transducer in the left ventricle is required for conscious and chronic studies, the theoretic risk of artifactual dysrhythmias exists. Careful analysis suggests that in reality the risk of these is low.

Sarazan, R; Mittelstadt, S; Guth, B; Koerner, J; Zhang, J; Pettit, S. *International Journal of Toxicology*. May 2011.

R. Dustan (Dusty) Sarazan to Receive SPS 2011 Distinguished Service Award

Dusty Sarazan DVM, PhD, will be recognized during the upcoming Safety Pharmacology Society Annual Meeting for his significant contributions toward the measurement of cardiovascular function.

If attending SPS, please be sure to attend Dr. Sarazan’s presentation, “Cardiovascular Safety Assessment of Drugs: Perspectives from a Career Spanning Pharma, CRO, and Technology Development” on Thursday, September 22 at 10:30 in the Brussels Room.

The Distinguished Service Award is given to honor an individual who has substantially contributed to the field of Safety Pharmacology. Additional information about this year’s award winner can be found in the 2011 SPS Program Guide.



Discovery of the Dual Orexin Receptor Antagonist [(7R)-4-(5-Chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3,-triazol-2-yl)phenyl]methanone (MK-4305) for the Treatment of Insomnia [Cox et al 2010]

A high incidence exists of insomnia characterised by unsatisfactory quality of sleep. It results in undesirable consequence during the waking period and in many cases its causes are poorly understood. Traditional treatments rely upon hypnotics which are non-specific and may cause residual sedation. Recent advances have been made in development of GABAA selective modulators although significant safety concerns exist over such compounds. Emerging knowledge of the specific role of the orexin (hypocretin) system in regulation of sleep provides a potential therapeutic target for management of insomnia, through antagonism of the orexin receptors OX1R and OX2R. This publication describes the synthesis and characterisation of chemical compounds showing desirable receptor binding, distribution and metabolism for use in insomnia (particularly brain penetration).

Telemetry was used as a functional assay to characterise effects of compounds being screened on a rat model of sleep function by measuring electrocortigram (ECoG) and electromyogram (EMG). F50-EEE or 4ET telemetry transmitters were implanted into adult male Sprague-Dawley rats (450-600g). Specific coordinates used are described for ECoG and EMG electrodes implanted into the nuchal muscles. Following two weeks' recovery time, recordings were carried out simultaneously for ECoG and EMG at 500Hz using Dataquest A.R.T. software (DSI.). Stored data from experiments was analysed using an automated sleep stage analysis program (Somnologica, Embla) based on movement in the cage, EMG and ECoG activity over 10 second epochs. Resulting analysis characterizes sleep into awake, light sleep, delta sleep and REM (rapid eye movement) sleep.

The use of telemetry to monitor activity, ECoG and EMG with subsequent analysis to determine sleep patterns is well established in sleep research. This publication describes a valuable practical application in a screening sequence to identify chemical compounds suitable to progress into development. In this instance MK-4305 was identified as a potent antagonist of OX1R and OX2R, which entered to phase III clinical trials for primary insomnia.

Cox,C; Breslin, M; Whitman, D; Schreier, J; McGaughey, G; Bogusky, M; Roecker, A; Mercer, S; Bednar, R; Lemaire, W; Bruno, J; Reiss, D; Harrell, C; Murphy, K; Garson, S; Doran, S; Prueksaritanont, T; Anderson, W; Tang, C; Roller, S; Cabalu, T; Cui, D; Hartman, G; Young, S; Koblan, K; Winrow, C; Renger, J; Coleman, P. *Journal of Medicinal Chemistry*. 2010, Vol. 53, No. 14.

New Product Announcement — Artifact-Free ECG with the Solid Tip Lead

Nearly artifact-free ECG is now possible without a thoracotomy using DSI's new Solid Tip Lead and associated surgical technique for large animals.

Developed in partnership with our customers, the technique involves placing a positive electrode on the abdominal side of the diaphragm near the apex of the heart and inserting the negative lead into a jugular and locating the Solid Tip in the vena cava just above the heart. The resulting ECG waveform resembles a lead II morphology with higher amplitude components and virtually no artifact! All of this is done without fluoroscopy, without a thoracotomy, and without placing anything directly onto or into the heart!

The Solid Tip Lead is available with the D70-PCT, D70-CCTP, D70-PCTP, and D70-PCTR transmitters – new or exchanged devices. It will also be available with DSI's new TruSense Device. The solid tip and modified lead jacket enables the following:

- Simple, atraumatic delivery of electrode to the vena cava
- Long-term residence in blood flow without negative effects

The Solid Tip Lead is constructed from high quality, clinical grade material. Contact DSI today to learn about the Solid Tip lead.



Ask DSI Technical Support

What is the recommended number of JET devices per Bluetooth receiver?

It is recommended that JET systems are configured as defined below

- 6 JET-EA-BP devices per Receiver
- 4-6 JET-3ETA-BP devices per Receiver
- 4 JET-5ETA-BP devices per Receiver

This configuration recommendation is due to environmental variations at sites. The recommendation of 4 devices per receiver is a conservative recommendation that will likely reduce environmental effects. Please note: this recommendation is more important when using many devices. If only using a total of 16 devices or fewer, then the 6 per receiver configuration is acceptable. However, there may be instances where 4 devices per receiver may be beneficial / needed if the environment is especially noisy.

How is Tau calculated in Dataquest A.R.T.?

The formula for Tau is where M is the slope of a linear fit of the natural log (ln) of pressure points from min dP/dt to a terminus. The terminus shall be set to 66% of the total pressure drop in the cycle. You may choose to include the point or not based upon a confidence value from the linear fit. Multiply the result by 1000 to change the units from seconds to milliseconds.

Can an Analog Output Matrix power supply work with a regular DSI matrix?

Yes, it will. The only difference may be that the power supply may not have the metal box installed around the power supply for shielding. The metal box is used to help shield the rest of the system from the electrical noise that the power supply makes. Otherwise, the power supply is identical to the one that the regular matrix uses.

How can I mark Ectopic/Arrhythmic beats with ECG PRO yet exclude them from Analysis?

In order to utilize ECG PRO, it is important to have the R marks placed correctly using the ECG Analysis Module. The Analysis Module marks Ectopic beats best when setting the QRS Detection to Negative within the Attributes.

Setting the QRS Detection to Negative within the Attributes:

1. Right-Click the graph and select Analyze [Attributes]
2. Click the QRS Detection dropdown and select Negative
3. Click OK
4. Check the checkbox to 'Re-analyze the channel.'
5. Choose the radio button for 'The entire Channel'
6. Click OK

Then, add arrhythmic cycles to the template graph and ana-

lyze the channel using the ECG PRO Template.

1. Right-click the ECG channel within the Primary graph page on a cycle to be added to the Template graph
2. Select Add Template Cycle
3. Right-click the ECG channel within the Primary graph page
4. Select Analyze [Entire Library]

To exclude these cycles from the analysis and obtain data for the remaining, normal ECG cycles:

1. Analyze the entire channel with QRS detect set to Negative
2. Analyze using your template
3. Setup the Scatter Delete marks method to Bad Data Marks
 - a. Select Options – Application Configuration – Review
 - b. Choose Bad Data Marks from the 'Scatter Delete Marks Method' dropdown box
4. Setup a Scatter graph of Match vs. Num
 - a. Select Setup – P3 Setup – Graph Setup
 - b. Choose Graph page 3 and enable the graph
 - c. Choose Scatter as the graph type
 - d. Select Num as X-axis: 0 to 300 (low to high scale)
 - e. Select Match as Y-axis: -10 to 150 (low to high scale)
 - f. Click Apply
5. Within Page 3 - Scatter graph, select the Free Form Select icon from the tool bar
6. Left-click-and-drag a loop around the point at 100 – basically selecting the point that are at 100 percent match
7. Right-click within the loop and select "Add Bad Data Marks to Selected Points"
8. Re-analyze the channel with the QRS detect set to Positive

Glucose Monitoring Solutions from DSI

DSI will soon be offering glucose monitoring solutions for both acute and chronic monitoring needs. DSI has been actively engaged with several companies experienced in developing meters and sensors.

We have gained valuable experience using a number of these products in our laboratory. We expect to complete distribution agreements for glucose monitoring products in the very near future.

Please contact your sales representative or DSI product manager, Chris Kolin (ckolin@datasci.com), for more information and to discuss your study needs.

Dean Franklin Young Investigator Award

DSI will be sponsoring a young investigator award at the American Physiological Society for a scientist specializing in *in vivo* research.

The Dean Franklin Young Investigator Award has been established in recognition of Franklin's role in the development of instrumentation to monitor physiological function in conscious research animals and humans. Concepts originally formulated by Dean Franklin continue to serve as the inspiration behind many of DSI's most technologically advanced physiological monitoring systems developed for today's nonclinical research.

The award recognizes a post-doctoral scientist or junior faculty member who is pursuing *in vivo* physiological research and is in the process of establishing an independent laboratory. The award recipient receives a travel award of \$1,500 to attend the annual Experimental Biology meeting in 2012 to present his/her work, and a DSI instrumentation starter kit (approximate value \$20,000).

The application deadline for next year's award will be early November and the award will be presented at the Experimental Biology meeting April 2012 in San Diego. Additional details will soon be available at www.the-aps.org.

Recent Publication: Attenuation of Isoproterenol-induced Cardiac Fibrosis in Transgenic Rat Harboring an Angiotensin-(1-7)-producing Fusion Protein in the Heart [Ferreira et al 2010]

The biology of the circulating renin-angiotensin (RAS) has been well studied, but the existence of local RAS in tissues is a more recent discovery. Study of local tissue RAS is made difficult due to the presence of the circulating RAS.

This publication describes the generation and study of a transgenic rat in which Angiotensin(Ang)-(1-7) producing fusion protein is over-expressed in myocardial tissue under control on the α -myosin heavy chain (α -MHC) promoter. Ang-(1-7) appears to possess significant cardio protective functions. The construct used contains a furin cleavage site and the protein expressed undergoes cleavage to yield Ang-(1-7) by the enzyme furin, which is not part of the circulating RAS. Four founder transgenic rats were produced from pronuclear microinjection and bred to homozygosity. All showed significant expression product in the heart with little or no expression in other tissues. Line TG(hA-1-7)L7301 showed optimal cardiac expression and was selected

for experiments which utilised hemizygous animals to eliminate possible non-specific genomic effects of the presence of the transgene construct.

Telemetry was used to measure blood pressure in transgenic and control (Sprague-Dawley rats) as part of a range of studies. Using telemetry provided a good example of its role in an integrative biology approach in understanding complex phenotypes. Miniature telemetry transmitters were implanted into the peritoneal cavity of transgenic and wild type rats at 8 weeks of age with the blood pressure catheter directly introduced into the abdominal aorta. Following return of normal diurnal blood pressure oscillations after surgery, recordings were made sampling at 200Hz for 10 seconds every 5 minutes over a 24 hour period. These studies revealed no significant differences in blood pressure and heart rate of the transgenic from the control rats.

In addition to telemetry studies of blood pressure in conscious rats, isolated perfused hearts were studied extensively in Langendorff preparations. This revealed increased contractile force and reduced incidence of reperfusion dysrhythmias after occlusion of the left anterior descending coronary artery for 15 minutes. Calcium handling was enhanced in isolated cell studies. Finally, challenge with isoproterenol caused less subendocardial fibrosis in the transgenic rat compared with the control and it was concluded that the cardioprotective effects seen in animals expressing Ang-(1-7) in the heart are independent of systemic blood pressure effects.

Ferreira, A; Castro, C; Guatimosim, S; Almeida, P; Gomes, E; Dias-Peixoto, M; Alves, M; Fagundes-Moura, C; Rentzsch, B; Gava, E; Almeida, A; Guimarães, A; Kitten, G; Reudelhuber, T; Bader, M; Santos, R. *Therapeutic Advances in Cardiovascular Disease*. April 2010.

Recent Publication: Comparative Analysis of Telmisartan and Olmesartan on Cardiac Function in the Transgenic (mRen2)27 Rat [DeMarco et al, 2011]

Telmisartan blocks the angiotensin type 1 receptor (AT1R) with a molecular structure resembling the peroxisome proliferator-activated receptor (PPAR)- γ agonists pioglitazone and rosiglitazone, improving insulin sensitivity. PPAR- γ agonists may also reduce vascular oxidative stress and inflammation. It has been proposed that PPAR- γ agonism may be beneficial in myocardial protection after ischaemia-reperfusion injury and ventricular hypertrophic response to pressure overload. The (mRen2)27 transgenic rat expresses renin at a tissue level and provides a model of hypertension, dyslipidaemia and insulin resistance. Telmisartan (2.0mg/kg daily) and olmesartan (2.5mg/kg daily) were administered to male Sprague-Dawley rats in drinking water from 7 weeks of age for 3 weeks: these doses were shown to be equipotent in their antihypertensive actions by telemetry studies. Miniature telemetry transmitters (PA-C40, Datasciences International) were implanted

into rats at 6 weeks of age with recording of systolic blood pressure at 0, 1, 2 and 3 weeks after commencement of treatment. Experimental animals were hemizygous for the transgene and wild type controls, treated with vehicle, telmisartan or olmesartan.

At the conclusion of the treatment period, rats were anaesthetized and the left ventricle catheterised with a pressure-volume catheter (1.9FG, Scisense) to measure baseline haemodynamics, systolic and diastolic functions. While under anesthesia, subjects were euthanized in accordance with the established protocol, tissues were assayed for Jak2 (prohypertrophic) protein, biochemical markers of myocardial tissue oxidative stress and histomorphology.

Telemetric measurement of blood pressure during the three week dosing period showed mean systolic blood pressure (SBP) in transgenic rats to increase from 154 ± 1 to 198 ± 6 mmHg

while those treated with telmisartan fell to 124 ± 1 mm Hg and olmesartan 130 ± 3 mm Hg. Wild type (control animals) had mean SBP of 117 ± 1 mm Hg which showed no significant change during the study. Both drugs showed similar effects in prevention of left ventricular hypertrophy (increase in cardiomyocyte size and fibrosis) and similar effects on left ventricular function, haemodynamics, oxidative stress markers and Jak2 production. It was concluded that AT1R blocking action of telmisartan is chiefly responsible for its beneficial effects in the TG (mRen2)27 rat model, rather than its PPAR- γ agonist activity.

DeMarco, V; Johnson, M; Habibi, J; Pulakat, L; Gul, R; Hayden, M; Tilmon, R; Dellsperger, K; Winer, N; Whaley-Connell, A; Sowers, J. *AJP - Heart and Circulatory Physiology*. November 2010.

Advanced Neural Monitoring Solutions

To better serve neuroscience researchers, DSI is representing Triangle BioSystems International (TBSI). TBSI is a developer and manufacturer of neurological research equipment for brain and nerve monitoring, recording and stimulation. This advanced neuro-technology hardware and software enables the acquisition of action potential signals (spikes) from individual brain cells (neurons), as well as low frequency field potential (EMG and EEG) signals in miniature tethered and wireless sub-assemblies. TBSI systems are designed to work with small animals such as birds and mice as well as larger animals such as rats, dogs and non-human primates for biological, medical, psychological studies, and pharmaceutical drug discovery.

We are excited about the opportunity for TBSI products to augment our CNS offerings and offer the increased bandwidth and channel counts that neuroscientists have been seeking.



TBSI's W series wireless neural headstage devices shown above.

UPCOMING MEETINGS

Safety Pharmacology Society

September 19-22, 2011

High Blood Pressure Research Council

September 20-24, 2011

Spanish Society for Neuroscience

September 28-30, 2011

AALAS

October 3-6, 2011

Association of Inhalation Toxicology

October 5-7, 2011

AAPS Annual Meeting

October 23 - 27, 2011

Academy of Surgical Research

October 27-29, 2011

American College of Toxicology

November 6-9, 2011

Society for Neuroscience

November 13-16, 2011

American Heart Association

November 13-15, 2011

American Epilepsy Society

December 2-6, 2011

British Pharmacological Society

December 13-15, 2011

ASM Biodefense & Emerging Diseases

February 26-29, 2012

Society of Toxicology

March 11-15, 2012

FCVB

March 30-April 2, 2012

Experimental Biology

April 21-25, 2012

American Thoracic Society

May 18-23, 2012

Visit www.datasci.com for the most current listing of upcoming DSI events.

New Product Announcement: RSC-1 – Telemetry Receiver for Specialty Applications

The RSC-1 receiver is designed in a small size to accommodate a variety of specialized cage configurations. The receiver is small enough to be placed in many locations where the RPC-1 and RMC-1 receivers are simply too large. Examples include metabolic cages, running wheels, treadmills, etc. The RSC-1 reception range and other performance characteristics are comparable to the RPC-1 receiver. The RSC-1 receiver is compatible with all standard DSI telemetry models.

The RSC-1 supports the Distributed Receiver Array (DRA) functionality. This makes the RSC-1 a good choice for applications requiring extended coverage such as Open Field tests. When used in conjunction with the Dataquest A.R.T. or Ponemah system, the DRA function allows up to 16 receivers to be associated with an individual subject.

The RSC-1 also incorporates support for an external antenna. This receiver is compatible with the Culex ring antenna that has been designed specifically to accommodate the Culex cages from BASi for

automated blood sampling applications.



A ring antenna designed specifically for automated blood sampling applications is supported by the RSC-1 receiver.

These antennas may be used with certain other devices such as plethysmograph chambers. Antennas may be designed by other companies or researchers, with DSI's support, to optimize telemetry performance in a variety of situations.



RSC-1 receiver: the smallest telemetry receiver available from DSI. Shown with RPC-1 receiver.

The DSI Monitor is published by DSI to keep you informed of new products, applications and ideas in the field of physiologic monitoring of laboratory animals.

If you have information that you would like to share with other readers, please contact DSI at papers@datasci.com.

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Edited by Tony Webb

Tony Webb is a British veterinary graduate with over 20 years experience in experimental surgery – he now works as a consultant in the field and is collaborating with DSI to produce regular newsletters.

DSI™