

RENAL DENERVATION

Millions of people—about one-third of the adult population in the developed world—suffer from hypertension. Despite widespread efforts to better diagnose and manage hypertension, a number of factors, including the complexity of the disease, patient noncompliance with complicated drug regimens, side effects of medications and drug ineffectiveness, have resulted in poor blood pressure control rates. An increase in renal sympathetic nerve activity has been shown to be a significant contributing factor in developing and maintaining hypertensive states. It is becoming clear that the development of new, device-based therapies to perform minimally invasive renal sympathetic denervation—from catheter-based drug delivery systems to sonic and RF ablation devices—can provide a distinct advantage in combating this major healthcare burden.

CBSET—SPECIALIZED EXPERTISE DEVELOPING DEVICE-BASED RENAL DENERVATION THERAPIES

IN VIVO: CBSET Inc. is a leader in the evaluation and development of novel diagnostic, therapeutic and imaging technologies, providing support for all phases of biomedical discovery and development research. CBSET has developed specialized expertise in the development and application of minimally invasive device-based interventional therapies for renal denervation, having performed more than 200 surgical and device-based pre-clinical procedures.

EFFICACY: Reduction of kidney norepinephrine (NEPI) content is a key biomarker for determining the efficacy of renal denervation. However, the analytical challenges present in quantitation of NEPI in the sub-endogenous range are significant. Physiological levels of NEPI are low and NEPI is inherently unstable and subject to rapid metabolic and non-metabolic oxidative degradation. Accurate measurement of NEPI in a down-regulated state is required to adequately compare the efficacy of novel technologies and therapies.

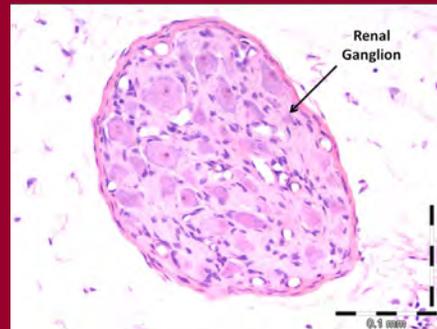
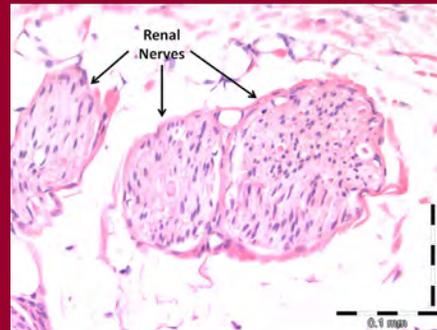
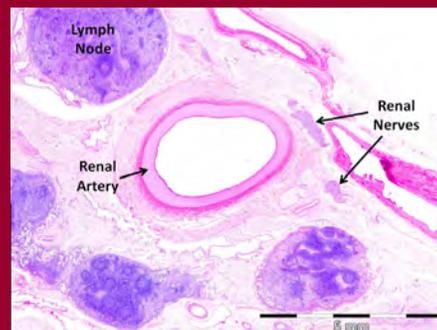
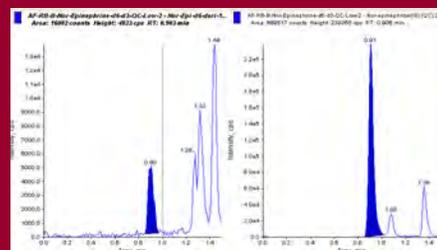
Historical bioanalytical methods of detection have employed high-pressure liquid chromatography coupled with electrochemical detection (HPLC-EC). These methods afford high sensitivity but lack mass unit specificity and are therefore subject to potential interferences from a large number of endogenous and exogenous compounds present in tissue. HPLC-EC sample preparation methods are complex, chromatographic run times are long (10+ min), and EC detector instability can complicate quantitation in these long analytical runs.

To address these complex analytical issues, CBSET has developed a novel HPLC-MS/MS assay to accurately quantify norepinephrine concentrations in porcine kidney tissue. This assay is specific, sensitive, stable, robust, and linear over 3 orders of magnitude; it significantly improves method performance and data reliability in the sub-endogenous range. This allows assessment of efficacy and aids in the differentiation and selection of the best treatments and therapies.

CORRELATE SAFETY AND EFFICACY: CBSET's board-certified pathologists employ novel histopathology methods to evaluate the time-course tissue response and pathophysiology of the renal arteries, renal nerves and kidneys following denervation procedures. These proven methods allow successful correlation of the depth and orientation of treatment (safety) with the location of nerves in the surrounding adventitia and the reduction in NEPI levels (efficacy) in the same animals. Successful correlation of safety and efficacy in CBSET's pre-clinical models allows faster and improved selection of new therapies and minimizes animal usage and overall program expenses.

THE CBSET PROCESS

1. Study Design/Development
2. Experimental Execution
3. Histopathology/Pathology
4. Data Analysis & Reporting



ABOUT CBSET

CBSET is an AAALAC accredited, not-for-profit, pre-clinical research organization dedicated to research, education, and the advancement of early-stage biomedical technologies. Our mission is to assist in methodologies uniquely suited for novel and innovative treatments for complex diseases. We offer a full range of GLP and non-GLP services, ranging from early product evaluation through lead optimization and pre-clinical safety, to physician assessment and training courses. We specialize in the development and application of techniques in the fields of cardiology, electrophysiology, orthopedics, wound healing, regenerative medicine, endoscopy/laparoscopy, drug and device delivery and safety, cellular therapy, and diagnostic imaging. Our world-renowned regulatory and scientific expertise helps transform early-stage concepts into novel therapies.

CBSET EXPERTISE

Our professionally trained staff and consultants provide expertise for all phases of biomedical discovery and development research including regulatory consulting, veterinary medicine, surgery and minimally invasive surgery, imaging, pharmacokinetics and drug metabolism, drug and device safety, pharmacology, lead optimization, and specialized histopathology and pathology. These individuals provide the basis for successful scientific collaborations, rapid concept advancements, unparalleled consultation services, and expert dissemination of information and findings to regulatory and scientific bodies.

CBSET offers a full range of GLP and non-GLP services, from early product evaluation through lead optimization and pre-clinical safety, to physician assessment and training courses. Our expertise includes:

- Stents/balloons
- Novel catheters/wires
- Robotic-assisted surgery
- Vessel sealing/closure devices
- Heart valve replacement/repair
- Cardiopulmonary bypass
- Beating heart technology
- Electrophysiology devices
- Tissue ablation devices
- Endovascular/NOTES surgery
- Laparoscopic surgery
- Orthopedic devices
- Novel surgical instruments
- Wound healing devices
- GLP training and regulatory consulting

CBSET FACILITIES

CBSET offers an unparalleled, GLP-compliant, 30,000 square foot state-of-the-art facility within minutes of Cambridge, Boston, and Logan International Airport. Our facility includes vivariums, catheterization/imaging labs, and full surgical suites containing the latest equipment for fluoroscopy, echocardiography (TEE/TTE), electrophysiology, IVUS, optical coherence tomography (OCT), endoscopy/laparoscopy, orthopedic surgery, and surgical video recording. CBSET offers dedicated labs for GLP-compliant SEM, specialty histopathology/pathology, metabolism and pharmacokinetics



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